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Investigating for an Association between Delirium and Autonomic Impairment

Dr Elaine A.M. Shanahan MB BCh BAO MRCPI

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Supervised by:
Dr Margaret O'Connor
Prof Tom Kiernan

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Abstract

Title: Investigating for an Association between Delirium and Autonomic Impairment

Author: Elaine Shanahan

Delirium is a common syndrome amongst acutely unwell older adults. It is associated with significant morbidity and mortality, yet it remains poorly researched in the literature. Several theories have been proposed to explain the development of delirium but despite this the pathophysiology remains poorly understood. My thesis aims to addresses one such theory that has been little researched in the past; could delirium be associated with autonomic impairment?

My thesis outlines the rationale for looking for such an association, including changes in cerebral perfusion and the role of acetylcholine.

My study had a prospective case-control design. Participants were recruited while they were an inpatient with an acute illness in University Hospital Limerick. Diagnostic and Statistical Manual of Mental Disorders 4th Edition (DSM-IV) and Delirium Rated Scale Revised 1998 (DRS-R98) were used to evaluate for delirium. When the participant was free of acute illness a number of tests of autonomic function were carried out and consisted of a Head-Up Tilt test (HUT), baroreflex sensitivity testing measured using Baroreflex Effectiveness Index (BEI), 24-hour blood pressure variability (BPV), nocturnal blood pressure dipping status and 24-hour heart rate variability (HRV) measurements. A subgroup analysis of those without pre-existing cognitive impairment was carried out.

During HUT the delirium group had a median decrease of 1mmHg (IQR 38.5) in systolic blood pressure compared to a median decrease of 17.5mmHg (IQR 20.75) in the control group (p=0.04). Increased delirium severity correlated with a reduction in the drop in systolic blood pressure during HUT (r_s= -0.42, p=0.03).

In those without pre-existing cognitive impairment, baroreflex sensitivity testing during HUT showed that increases in blood pressure were not followed by an appropriate corrective reduction in heart rate with a mean BEI of 36.87% (SD 22.26) in those with delirium and 56.03% (SD 23.04) in those without delirium (p=0.05).

Nocturnal dipping status differed between the two groups during the subgroup analysis. 58.3% (7) of delirious participants were reverse dippers, 33.3% (4) were non-dippers and 8.3% (1) had a normal dipping pattern. No participant was an extreme dipper. In the control group no participant was a reverse dipper, 57.1% (4) were non-dippers, 14.3% (1) had a normal dipping pattern and 28.6% (2) were extreme dippers (p=0.01).

BPV was measured by average real variability (ARV). In those without pre-existing cognitive impairment mean ARV was 13.81 (SD 5.98) in the control group and 9.69 (SD 2.75) in the delirium group (p=0.05).

HRV was measured using a 24-hour holter monitor. No difference was detected between the two groups.

This study identifies differences in autonomic function between delirious participants and non-delirious controls, particularly when the impact of pre-existing cognitive impairment is excluded. This is the first study to look at several components of autonomic function in delirium and thus can provide insights into physiological

abnormalities present during, or contributing to delirium and can help to inform future research.

Declaration

I declare that this thesis is my own work and that the data presented is accurate. I declare that this thesis has not been submitted for any other award or degree at this or any other University.

Elaine Shanahan

_____ Date: / /

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Publications and Presentations

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Conference Presentations

Reduced Baroreceptor Sensitivity in Patients with Recent Delirium; Elaine Shanahan, Sheila Ryan, Aine Costelloe, Tina Sheehy, Catherine Peters, Declan Lyons, Margaret O'Connor; Irish Gerontology Society Conference Cavan, September 2018

Abnormal Diurnal Blood Pressure Variability in Patients with Recent Delirium; Elaine Shanahan, Sheila Ryan, Aine Costelloe, Tina Sheehy, Tom Kiernan, Catherine Peters, Declan Lyons, Margaret O'Connor; British Geriatric Society Conference London, November 2018

Autonomic Impairment and its Manifestations in Patients with Delirium; Elaine Shanahan, Sheila Ryan, Aine Costelloe, Tina Sheehy, Catherine Peters, Declan Lyons, Margaret O'Connor; Irish Gerontology Society Conference Cork, September 2019

Publications

Reduced Baroreceptor Sensitivity in Patients with Recent Delirium; Elaine Shanahan, Sheila Ryan, Aine Costelloe, Tina Sheehy, Catherine Peters, Declan Lyons, Margaret O'Connor; Age and Ageing, Volume 47, Issue suppl_5, 1 September 2018, Pages v13–v60; (abstract publication)

Abnormal Diurnal Blood Pressure Variability in Patients with Recent Delirium; Elaine Shanahan, Sheila Ryan, Aine Costelloe, Tina Sheehy, Tom Kiernan, Catherine Peters,

Declan Lyons, Margaret O'Connor; Age and Ageing, Volume 48, Issue suppl_1, February 2019; (abstract publication)

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The Association between Delirium and Autonomic Dysfunction-A Systematic Review; Elaine Shanahan, Sheila Ryan, Catherine Peters, Declan Lyons, Margaret O'Connor; Being updated for submission

Is Delirium a Manifestation of Sympathetic Overactivity? A Pilot Study Comparing Head –Up Tilt Results in Delirious and Non-Delirious Participants; Elaine Shanahan, Sheila Ryan, Catherine Peters, Declan Lyons, Margaret O'Connor; Under revision for submission to BMC Geriatrics

Educational Presentations

Assessment and Management of Acute Confusion; Presentation as part of Intern Training Programme University Hospital Limerick, July 2017

Autonomic Dysfunction; Presented at the North Dublin Postgraduate Educational Meeting, February 2019

List of Text Abbreviations

A	
ABPM	Ambulatory Blood Pressure Monitor
AD8	Eight Item Interview to Differentiate Aging and Dementia
APACHE II	Acute Physiology and Chronic Health Evaluation II score
B	
BEI	Baroreflex Effectiveness Index (The proportion of changes in blood pressure followed by an appropriate change in heart rate)
BEI-Down	Baroreflex Effectiveness Index During Down Trends in Blood Pressure (The proportion of reductions in blood pressure followed by an appropriate increase in heart rate)
BEI-Up	Baroreflex Effectiveness Index During Up Trends in Blood Pressure (The proportion of increases in blood pressure followed by an appropriate decrease in heart rate)
BP	Blood Pressure
bpm	Beats Per Minute
BRS	Baroreflex Sensitivity
BPV	Blood Pressure Variability
C	
CAM	Confusion Assessment Method
CAM-ICU	Confusion Assessment Method for Intensive Care Unit
CI	Confidence Interval
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease

CSH	Carotid Sinus Hypersensitivity
CSF	Cerebral Spinal Fluid
D	
DBP	Diastolic Blood Pressure
DMSS	Delirium Motor Subtyping Scale
DRS-R98	Delirium Rating Scale-Revised 1998
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4th Edition
E	
ECG	Electrocardiography
F	
FI	Frailty Index
G	
GIT	Gastrointestinal Tract
H	
HF	High Frequency
HRV	Heart Rate Variability
HTN	Hypertension
HUT	Head-Up Tilt
Hz	Hertz
I	
ICU	Intensive Care Unit
IQR	Interquartile Range

L	
LF	Low Frequency
M	
MAP	Mean Arterial Pressure
MoCA	Montreal Cognitive Assessment
N	
NICE	National Institute for Health and Care Excellence
NN	Normal-to-Normal (sinus) beats
O	
OH	Orthostatic hypotension
OHTN	Orthostatic hypertension
P	
POTS	Postural Orthostatic Tachycardia Syndrome
R	
RR interval	The time between two consecutive R waves in the cardiac cycle
S	
SBP	Systolic Blood Pressure
SD	Standard Deviation
SPSS	Statistical Package for Social Sciences
V	
vs	Versus

Chapter 1:
Introduction

1.0 Introduction to Thesis

This thesis aims to look for evidence to support the hypothesis that there is an association between delirium and autonomic impairment.

I will begin in Chapter 1 by providing an introduction to delirium epidemiology, clinical features and treatment. I will discuss the current theories that aim to explain the pathophysiology of delirium. Some of these theories form the basis for the hypothesis of this thesis. I will then provide an overview of the autonomic nervous system including physiology, clinical presentation of autonomic failure and some diagnostic tests used to evaluate for the presence of autonomic impairment.

Taking the information presented in Chapter 1 into account, Chapter 2 outlines the rationale for looking for an association between delirium and autonomic impairment. It contains a literature review looking for previous research to support the hypothesis.

Chapter 3 outlines the methods used in a prospective case-controlled study that aimed to test the hypothesis. This study forms the main component of this thesis. Chapter 4 contains the results of this study and Chapter 5 discusses the results in the context of current available evidence and offers suggestions for future directions of study.

1.1 Introduction to Delirium

Delirium is a condition associated with a global disturbance in cognition, inattention and perceptual disturbances, that is acute in onset and fluctuates in severity (Burns *et al.* 2004). Delirium is associated with adverse outcomes including increased in-hospital mortality, twelve month mortality, length of hospital stay and rates of institutionalisation (Siddiqi *et al.* 2006; Witlox *et al.* 2010). Delirium has been shown to be associated with cognitive decline, particularly in individuals with dementia (Fong *et al.* 2009) and to be independently associated with poor functional outcomes after hip fracture (Marcantonio *et al.* 2000). Mortality rates have been reported to increase by 11% for every 48 hours of delirium (Gonzalez *et al.* 2009).

Delirium can be described as a syndrome of acute brain failure (Daly 1980), for which there are numerous risk factors, causes and a myriad of underlying pathophysiological processes. Pre-existing chronic brain conditions make an individual more vulnerable to manifesting delirium, even with minor insults.

1.2 Epidemiology of Delirium

Delirium occurs commonly in hospitalised older adults. The incidence rate varies according to the population studied with an incidence of between 10% and 31% in medical inpatients (Siddiqi *et al.* 2006), up to 80% in some Intensive Care Unit (ICU) populations (Cavallazzi *et al.* 2012), 45% in oncology wards and 16% to 62% in patients with acute hip fracture (Kyziridis 2006). Delirium is also common in nursing home residents with an incidence of 20.7 per 100 person-years reported (Boorsma *et al.* 2012). Delirium often remains undiagnosed with one Irish prevalence study reporting up to half of cases remaining undiagnosed (Ryan *et al.* 2013).

1.3 Pathophysiology of Delirium

Various theories exist to explain the underlying pathophysiology of delirium but no single definitive mechanism has been shown. In certain cases the cause can be attributed to direct brain insults such as hypoxia, encephalitis, cerebral haemorrhage or cerebral infarction (MacLullich *et al.* 2008). However, in other cases such infections in remote sites, it is more difficult to ascertain the mechanism that leads to delirium.

Delirium is more prevalent in older adults than their younger counterparts. It is therefore likely that the physiology of brain ageing is an important factor in delirium development (Flacker and Lipsitz 1999). It is known that in normal older adults there is cerebral atrophy (Skullerud 1985) and reduced cerebral perfusion (Krausz *et al.* 1998; Parkes *et al.* 2004), with impaired mechanisms that maintain cerebral blood flow during fluctuations in blood pressure (Wagner *et al.* 2012). There is also age related neuronal loss particularly in the cerebral cortex (Walhovd *et al.* 2011). This altered physiology of the brain with ageing is compounded by the increased prevalence of brain disorders such as stroke, small vessel disease and Alzheimer's pathology, thereby increasing the vulnerability of the brain to insults. Neurofilament light is a biomarker for neuroaxonal injury. Serum and CSF levels are higher in postoperative hip fracture delirious compared to non-delirious patients (Halaas *et al.* 2018). This suggests that delirium pathophysiology involves neuronal injury.

Some of the main mechanisms proposed for delirium development are outlined below.

1.3.1 Inflammatory Theory

Infection at remote sites is one of the most common precipitants of delirium. Circulating inflammatory mediators, released in response to a systemic illness, can interact with cerebral neurons resulting in activation of endothelial cells and release

of prostaglandins and pro-inflammatory cytokines. This results is low level inflammation in the brain and could lead to the changes in cognitive function that occur in delirium (MacLullich *et al.* 2008).

Several studies that look at levels of inflammatory markers in delirious patients support the inflammatory theory. C-Reactive Protein is an acute phase protein and is used widely is clinical practice as a marker of inflammation and infection. It has been shown to be more markedly raised in certain patients with delirium compared to those without delirium (Ritchie *et al.* 2014). Interlukin-6 levels are higher in delirious than non-delirious hip fracture patients (van Munster *et al.* 2010). Administration of Interlukin-2 can result in the development of delirium (Flacker and Lipsitz 1999).

1.3.2 Neurotransmitter Abnormalities

Acetylcholine is known to be involved in consciousness, attention and memory and a deficiency in acetylcholine is therefore thought to be involved in the pathophysiology of delirium. Its levels normally decline with age, making older adults more susceptible to developing delirium (Ali *et al.* 2011). Administration of anti-cholinergic agents can induce delirium (Flacker and Lipsitz 1999) and increased anticholinergic activity has been shown to be associated with the development of delirium (Tune *et al.* 1981; Golinger and Tune 1987). However, serum anti-cholinergic activity levels can overlap significantly between delirious and non-delirious patients suggesting that other factors are involved (Flacker and Lipsitz 1999).

Serotonin is an excitatory neurotransmitter in the brain involved in wakefulness, mood and cognition (Flacker and Lipsitz 1999). It is derived from the amino acid precursor tryptophan (Lewis and Barnett 2004). Tryptophan crosses the blood brain barrier via completion with other large amino acids for the sodium independent LNAA transporter type 1 (Pandharipande *et al.* 2009). Thus if the proportion of another amino acid changes due to acute illness it can lead to reduced cerebral tryptophan and

therefore reduced serotonin. Studies have shown reduced levels of tryptophan (Robinson *et al.* 2008) and an altered ratio of tryptophan to other large amino acids (Pandharipande *et al.* 2009) in patients with delirium. Melatonin is a tryptophan derived substance involved in the regulation of the sleep-wake cycle. Melatonin therapy has been shown to be effective in the prevention of delirium in patients with hip fracture (Al-Aama *et al.* 2011) and treatment of post-stroke delirium (Ohta *et al.* 2013). This further supports the involvement of tryptophan in the pathophysiology of delirium.

Dopamine levels can be increased during times of oxidative stress such as during an acute illness. This dopamine excess can lead to some of the features of delirium including hallucinations and delusions (Ali *et al.* 2011). The dopamine excess theory is supported by studies comparing homovanillic acid levels in patient with and without delirium. Homovanillic acid is the main dopamine metabolite and plasma levels show a significant correlation with cerebrospinal fluid (CSF) concentrations. Increased CSF homovanillic acid concentrations are found in delirious patients (Ramirez-Bermudez *et al.* 2008). Plasma homovanillic acid levels are higher in delirious Alzheimer's dementia patients than non-delirious Alzheimer's dementia controls (van der Cammen *et al.* 2006).

A combination of these neurotransmitter abnormalities may be involved in the development of delirium.

1.3.3 Cortisol-Neuroendocrine Theory

There is some evidence to support the hypothesis that elevated levels of cortisol may be involved in the pathogenesis of delirium. Increased stress, as a response to acute illness, can cause activation of the sympathetic nervous system, one of the effects of which is the release of cortisol. Excess cortisol has a negative impact on hippocampal function and memory (Ali *et al.* 2011). Higher serum cortisol levels (Kazmierski *et al.*

2013) and a reduction in the normal diurnal variation in cortisol have been found in post-operative patients with delirium (Hall *et al.* 2016). Serum cortisol levels have been correlated to delirium severity in patients after an acute coronary syndrome (Colkesen *et al.*). CSF cortisol has also been shown to be higher in delirious than non-delirious patients (Pearson *et al.* 2010).

1.3.4 Cerebral Blood Flow and Oxidative Stress

A reduction in cerebral blood flow could cause insufficient oxygenation of cerebral cells leading to cerebral dysfunction (Ali *et al.* 2011). Measures of oxygenation and oxidative stress have been found to be worse in patients with delirium than in controls (Seaman *et al.* 2006). Neopterin is a marker of oxidative stress. Levels are higher in abdominal surgery patients who develop delirium (Miao *et al.* 2018).

Cerebral blood flow has been shown to be lower in patients during a delirious episode than after resolution (Yokota *et al.* 2003; Fong *et al.* 2006). In particular, cortical hypoperfusion has been identified using single-photon emission computed tomography (SPECT) scanning (Haggstrom et al. 2017). Continuous regional cerebral oxygenation monitoring using near-infrared spectroscopy suggests that cerebral autoregulation may be altered in delirium (Lee et al. 2018).

Given the broad range of precipitants for delirium and the varied way in which it can present it is likely that delirium arises as a result of several of the above factors interacting, possibly with a common end pathway (van Munster and de Rooij 2014).

1.4 Diagnosis of Delirium

The Diagnostic and Statistical Manual of Mental Disorders (DSM) produced by the American Psychiatric Association, provides the diagnostic criteria for delirium. The

assessment has to be carried out by a trained professional following standardised testing.

There are numerous different assessment scales in use in the clinical or research setting. The scales have a wide range of functions including delirium screening and diagnosis, assessment of arousability and screening for pre-morbid cognitive impairment.

One of the most common delirium screening tools used in clinical practice is the Confusion Assessment Method (CAM). It is well validated with a sensitivity of 94-100% and specificity of 90-95% (Wei *et al.* 2008). It has been adapted for use in the Intensive Care Setting (CAM-ICU) and is included in The National Institute for Health and Care Excellence (NICE) 2010 guidelines for delirium diagnosis (NICE 2010). The use of the CAM does however require appropriate training and can be difficult to apply quickly in the clinical setting.

The 3D-CAM (3-Minute Diagnostic Assessment for Delirium) is based on the CAM algorithm. It stipulates observations and brief cognitive tests that should be used to inform diagnosis of each of the four criteria of the CAM. As the name suggests, it takes 3 minutes to complete, making it much quicker than the CAM. It has a sensitivity of 95% and specificity of 94% when compared to diagnosis made by DSM-IV criteria (Marcantonio *et al.* 2014).

One of the best scales for quantifying delirium severity is the Delirium Rating Scale-Revised 1998 (DRS-R98). This is based on the DSM criteria. It is more commonly used in the research setting as it is cumbersome to use in clinical practice.

The 4AT is a newer screening tool. It is a validated, practical tool that is quick to perform and requires minimal training. It is a simple tool to implement in clinical

practice, although it's sensitivity (89.7%) and specificity (84.1%) are less those of the CAM (Bellelli *et al.* 2014).

1.5 Clinical Features of Delirium

Delirium develops over a short period of time, hours to days, and fluctuates in severity.

Below are the most common features of delirium (Farley and McLafferty 2007; Saxena and Lawley 2009):

1. Altered consciousness
   reduced arousal or hyper-vigilant
2. Inattention
   reduced ability to concentrate and process information or is easily distracted
3. Disorganised thinking
   confused, incoherent speech or lack of relevance of speech
4. Perceptual disturbance
   hallucinations (predominately visual) or illusions
5. Disturbance of sleep wake cycle
6. Reduced orientation to time, place and person
7. Disturbed visuospatial ability
   getting lost in familiar environment, impaired intersecting pentagons or clock drawing (bearing in mind that clock drawing involves numerous interacting cognitive processes including attention, planning and executive function)
8. Urinary incontinence
9. Gait impairment

Inattention is a cardinal feature of delirium. Inattention can be obvious during a comprehensive patient assessment. Specific tests for inattention include the Months of the Year Backwards test. It is one of the most useful bedside tests for inattention (O'Regan *et al.* 2014). The test is commenced by asking the patient to recite the months forward to ensure capacity to understand and engage in testing. You then ask the

patient to recite the months backwards starting with December. Inattention is considered present if they are unable to recite the months backwards as far as June.

A range of motor subtypes of delirium have been described and include hyperactive delirium with increased level of activity with agitation, wandering, fidgeting or restlessness and hypoactive delirium with decreased activity and few spontaneous movements, decreased speed of actions, decreased amount or speed of speech, less reactive to their environment or detached from surroundings. Hypoactive delirium often goes unrecognised on medical wards and at home. (Meagher 2009)

1.6 Factors that Precipitate or Predispose to Delirium

There are numerous factors that can precipitate or cause delirium (Saxena and Lawley 2009). The most common precipitating events for delirium can be grouped based on a modified version of the Delirium Etiology Checklist.

Table 1 shows common precipitating factors for delirium.

Table 1: Precipitating Factors for Delirium

Drug Intoxication or adverse effect	Alcohol Benzodiazepines Opioids Sedatives Anitcholinergics Antipsychotics Carbon monoxide poisoning Polypharmacy
Drug Withdrawal	Alcohol Hyponotics Benzodiazepines
Metabolic/Endocrine Disturbances	Electrolyte disturbances (e.g. hyponatraemia and hypercalcaemia) Hyper/hypoglycaemia Dehydration Hypo/hyperthyroidism Addisonian crisis B12, folate, thiamine deficiency Hypoxia or hypercapania
Cardiovascular	Myocardial infarction Cardiac failure
Systemic infection	At any other site, commonly urinary tract or respiratory tract
Cerebrovascular	Intracerebral haemorrhage Ischaemic stroke
Organ Insufficiency	Renal failure Liver failure
Central Nervous System (CNS)	Seizures Meningitis/encephalitis
Other	Multiple co-morbidities Constipation Urinary retention Pain Hypo/hyperthermia Anaemia Shock Surgery Change in environment Bladder catheter Sleep deprivation Terminal Illness/cancer Malnutrition
Demographics	Older Age Lower educational level Male

1.7 Treatment of Delirium

The National Institute for Health and Care Excellence provide guidance for the treatment of delirium (NICE 2010). Identification and treatment of the underlying precipitants is essential. Delirious patients require continuous reassurance and reorientation. Involvement of family or carers is recommended. Patients should not move between wards or rooms unless absolutely necessary. Good sleep hygiene should be promoted. Treatment of the precipitating acute medical illness is required for the resolution of delirium.

1.7.1 Antipsychotics

Where patients have severe agitation or distress, delirium may require pharmacological management to allow for the delivery of essential medical treatment. Short term (less than on week) use of anti-psychotics are considered for the treatment of distressed patients, who are a danger to themselves or others. Anti-psychotics should be used in caution in patients with Parkinson's Disease and be avoided completely in Lewy Body Dementia. It is widely accepted in clinical practice that antipsychotics reduce agitation and distress in delirious patients. Despite this the evidence supporting the routine use of antipsychotics in clinical practice is lacking. A recent systematic review and meta-analysis (Neufeld *et al.* 2016) found that antipsychotic use was not associated with improved delirium severity, delirium duration, mortality or length of stay. The quality of studies included was poor. A well conducted randomised controlled trial in a high risk hospital population is required to inform practice.

The choice of antipsychotic used can be tailored based on their sedative effects and available route of administration. Quetiapine (oral option only) and olanzapine (useful oral dissoluble wafer formulation) are more sedating whereas haloperidol and risperidone are less so. Haloperidol is available for intramuscular use. Quetiapine

would be accepted as the least likely to aggravate Parkinson's disease, although all antipsychotics should be avoided in Lewy Body Dementia.

Where anti-psychotics are used it should be for the shortest duration and at the lowest effective dose.

1.7.2 Benzodiazepines

Benzodiazepines are less effective than antipsychotics for the treatment of delirium and have been shown to worsen delirium (Lonergan *et al.* 2009). They are also more likely to cause over-sedation (Attard *et al.* 2008). They have a particular role in certain circumstances such as alcohol withdrawal, benzodiazepine withdrawal or for managing severe agitation in patients with Lewy Body Dementia. Benzodiazepines are also useful as an adjunct to antipsychotics for severe agitation where patients are a danger to themselves or others. Lorazepam, as a short acting benzodiazepine, is a suitable choice in this situation (Saxena and Lawley 2009). Longer acting benzodiazepines such as diazepam or chlordiazepoxide are useful for alcohol withdrawal. In the settling of seizure related delirium, benzodiazepines are a better option as antipsychotics lower seizure threshold and should be avoided.

1.7.3 Acetylcholinesterase Inhibitors

Acetylcholinesterase inhibitors are used in the treatment of Alzheimer's dementia (McGleenon et al. 1999). Rivastigmine has been associated with increased mortality in ICU patients (Van Eijk *et al.* 2011) and currently has no place in the routine treatment of delirium. In the settling of delirium associated with Lewy Body dementia, rivastigmine has however been shown to be beneficial in treating some symptoms of delirium (Saxena and Lawley 2009).

There is no evidence to support the use of donepezil in the treatment of delirium. Studies evaluating the effect of donepezil in the prevention of postoperative delirium have failed to show a significant benefit over placebo (Liptzin et al. 2005; Sampson et al. 2007; Marcantonio et al. 2011). The studies however have small sample sizes and were likely insufficiently powered to detect a significant difference.

1.7.4 Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2 receptor agonist that provides sedation, modest analgesia and reduces anxiety with minimal respiratory side effects. The pattern of sedation of alpha-2 agonists is quite different from that of other sedatives in that patients can be aroused readily and their cognitive performance on psychometric tests is usually preserved. Moreover, respiratory depression is less frequent. The most notable adverse effect is bradycardia. Alpha-2 agonists lack anticholinergic activity and promote a normal sleep pattern (Giovannitti *et al.* 2015).

Dexmedetomidine is in routine clinical use in the ICU setting. It is indicated for patients requiring mild sedation, to a level where they remain responsive to verbal stimuli (Scott-Warren and Sebastian 2015). Nocturnal dexmedetomidine use is associated with more delirium free days in ICU patients compared to placebo (Skrobik et al. 2018). It is also associated with a lower delirium prevalence than that of sedation with midazolam. The dexmedetomidine group did however have a higher rate of bradycardia but a lower incidence of tachycardia and hypertension (Riker *et al.* 2009).

1.7.5 Melatonin

Some recent attention has been given to the role of melatonin in the development and treatment of delirium. Melatonin is a hormone produced by the pineal gland. It is involved in regulation of the sleep-wake cycle. Delirious patients may have lower levels of melatonin or a disruption of the normal circadian pattern of melatonin. Post-

operative plasma melatonin levels are independently associated with the subsequent development of delirium (Chakraborti *et al.* 2015). Chakraborti et al performed a systematic review of the available evidence for the use of melatonin in the treatment of delirium. They identified one randomised controlled trial looking at delirium treatment and two looking at prevention. Incidence rates of delirium were lower in those treated with melatonin in the prevention studies. Delirium was successfully treated in 58% of patients in the treatment study. This was primarily a prevention study with all patients who developed delirium commenced on melatonin, there was therefore no comparative treatment group.

1.8 Delirium Summary

Delirium is a serious illness that presents with acute cerebral dysfunction. It is associated with adverse outcomes such as increased mortality and functional impairment leading to hospitalisation. The underlying pathophysiology is poorly understood and is likely multifactorial. The benefits of treatment have been poorly defined due to the difficulties in performing a stringent randomised controlled trial in a group of frail unwell older people, often with multiple co-morbidities and polypharmacy. The poorly understood underlying pathophysiology and the lack of evidence for effective treatments, compounded by the high prevalence and serious consequences of delirium, should prioritise this area for further study.

1.9 Introduction to the Autonomic Nervous System

The autonomic nervous system controls involuntary, physiological processes in the body including respiration, endocrine and exocrine glands, bladder contractility, digestion and cardiovascular function (McCorry 2007). The autonomic nervous system consists of afferent, connector and efferent neurons. The afferent neurons originate in effector organs and travel to the central nervous system (CNS) where they are integrated via connector neurons (Snell 2010). Responsible areas of the brain include the hypothalamus and the brain stem (McCorry 2007). A response is generated through impulses to the effector organs via efferent pathways (*Snell 2010*).

Efferent pathways, as shown in Figure 1, are made up of preganglionic and postganglionic neurons. The preganglionic neuron originates in the CNS in the lateral horn of the brainstem or spinal cord. Its axon synapses with the postganglionic neuron, which is located outside the CNS. The postganglionic neuron innervates the effector stem organ (McCorry 2007).

There are two divisions of the autonomic nervous system-the sympathetic nervous system and parasympathetic nervous system. Many organs have input from both systems with the sympathetic and parasympathetic systems having antagonistic effects on the organ (Snell 2010).

Figure 1: Efferent Pathways and Neurotransmitters of the Autonomic Nervous System

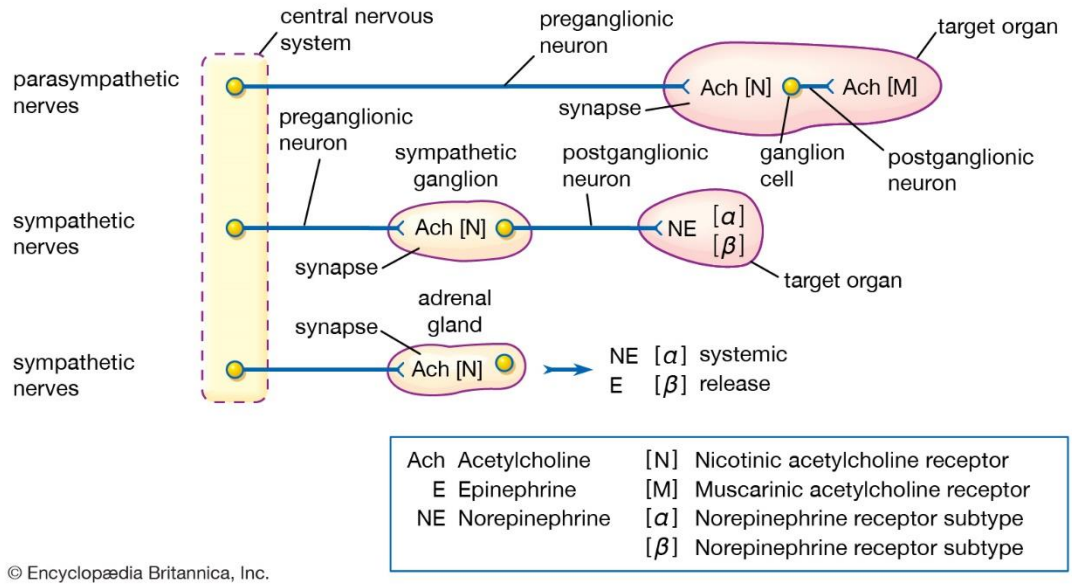


Figure 1 shows the efferent pathways of the autonomic nervous system and the neurotransmitters released at each synapse. Norepinephrine=noradrenaline, epinephrine=adrenaline. Ach=acetylcholine. Reprinted from Encyclopædia Britannica. Available at https://www.britannica.com/science/preganglionic-neuron/media/474696/1154. Accessed March 2019.

1.9.1 Sympathetic Nervous System

The sympathetic nervous system is the larger of the two parts of the autonomic nervous system and is present in the heart, lungs, blood vessel walls, hair follicles, sweat glands and many abdominal organs. It is involved in 'the flight or fight' response or in the preparation of the body for an emergency. It increases heart rate, constricts blood vessels of the skin and intestine, dilates skeletal muscle vasculature, increases blood pressure, dilates pupils, dilates the bronchi, inhibits smooth muscle contraction and closes sphincters of the bladder and bowel (Snell 2010). It also controls ejaculation and causes hepatic glycogenolysis and glucose release (McCorry 2007).

Preganglionic nerve bodies of the sympathetic nervous system are in the intermediolateral horn of the spinal cord from T1 to L2. Their neurons synapse with the sympathetic ganglia which are located adjacent to the spine. The neurotransmitter acetylcholine is involved in the transmission (Figure 1). The postganglionic neurons then travel to the effector organ. In most cases the postganglionic neurons release the neurotransmitter noradrenaline. Some nerve endings, particularly those transmitting to sweat glands and the blood vessels in skeletal muscles, release acetylcholine (McCorry 2007).

Figure 2 shows the organ innervations of the sympathetic nervous system.

1.9.2 Parasympathetic Nervous System

The parasympathetic nervous system is involved in conserving energy. It slows the heart rate and increases peristalsis and glandular activity. In addition, it constricts the pupils, controls erectile function, contracts the bladder wall and opens sphincters (McCorry 2007; Snell 2010).

Preganglionic nerve bodies of the parasympathetic nervous system are located in the brain stem and sacral part to the spinal cord. Parasympathetic ganglia are located in the effector organs (Figure 1). Both the preganglionic and postganglionic neurons release acetylcholine (McCorry 2007; Snell 2010).

Figure 3 shows the organ innervations of the parasympathetic nervous system.

Figure 2: Sympathetic Nervous System

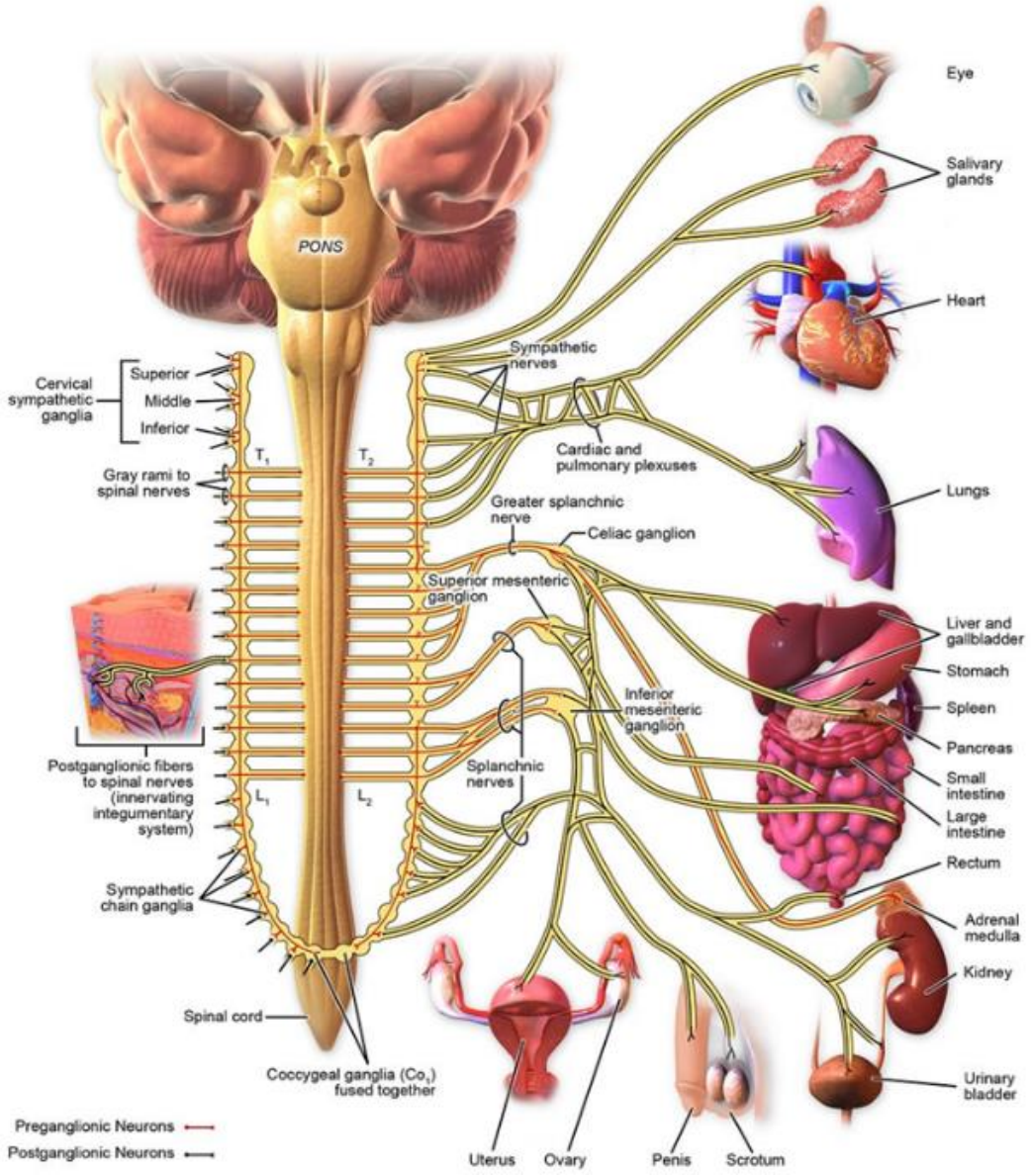


Figure 2 shows the innervation of the sympathetic nervous system. Reprinted from the Merck Manual Professional Version. Available at http://www. merckmanuals.com/professional. Accessed January 2019.

Figure 3: Parasympathetic Nervous System

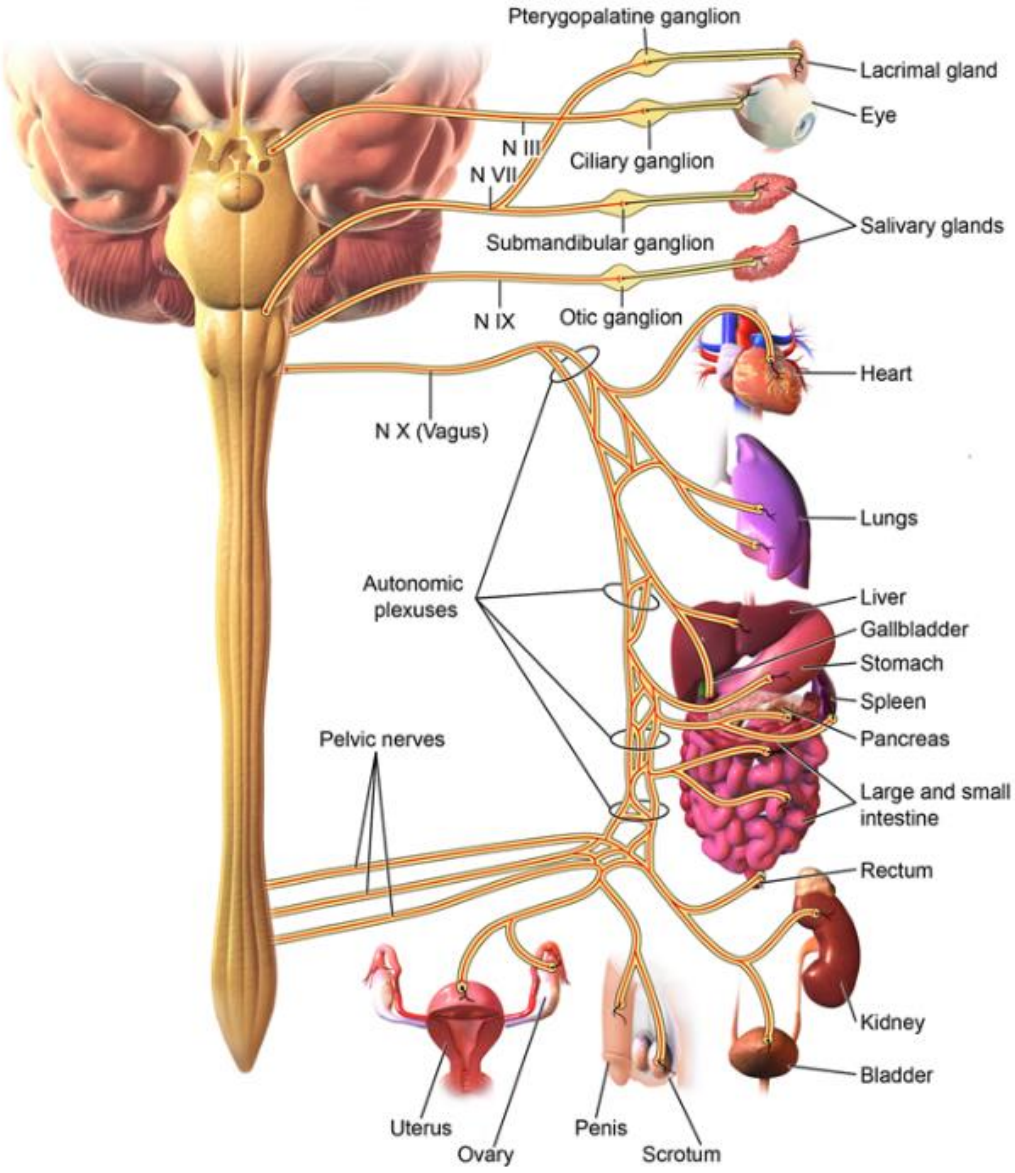


Figure 3 shows the innervation of the parasympathetic nervous system. Reprinted from the Merck Manual Professional Version. Available at http://www. merckmanuals.com/professional. Accessed January 2019.

1.9.3 Baroreceptor Function

Baroreceptors are stretch-sensitive nerve fibres that are mainly located in the carotid sinuses and in the aortic arch. Additional baroreceptors are located in the heart and pulmonary vessels and are referred to as cardiopulmonary receptors. Baroreceptors form part of a negative feedback loop with the medulla that functions to maintain mean arterial pressure (MAP). Afferent fibres travel from the baroreceptors to the medulla, while efferent fibres travel from the medulla to the heart and smooth muscle of blood vessels via the sympathetic and parasympathetic nervous systems. An increase in MAP activates the baroreceptors. This leads to a reduction in sympathetic outflow to the heart and blood vessels. A reduction in MAP, as shown in Figure 4, relieves the stretch on the baroreceptors, increases sympathetic output and causes vasoconstriction, increased cardiac output and an increase in MAP (Kougias *et al.* 2010).

Figure 4: Baroreceptor Function

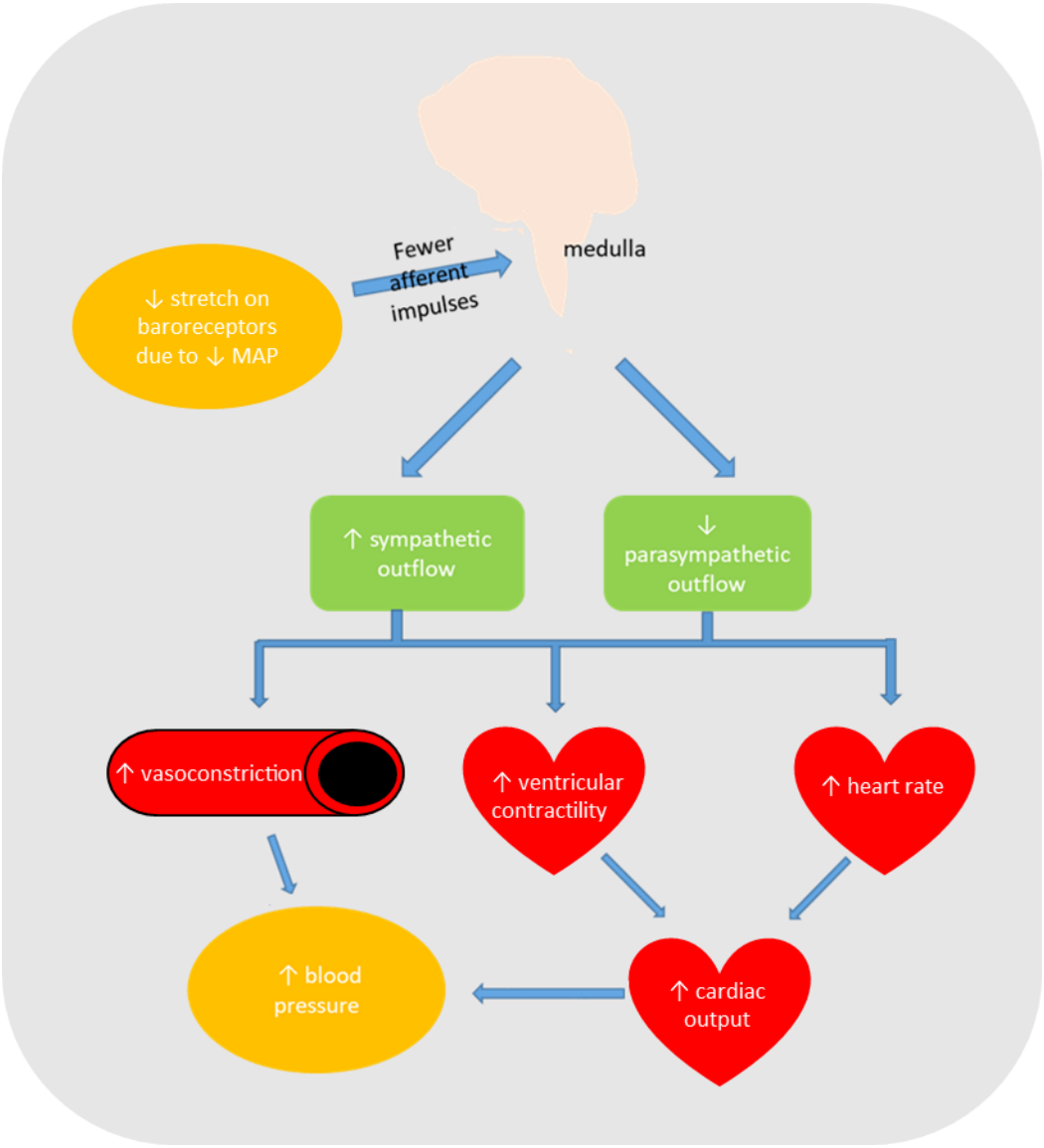


Figure 4 contains a schemata explaining the role of baroreceptors when mean arterial pressure (MAP) decreases. The reverse occurs when MAP increases.

1.10 Features of Autonomic Impairment

Symptoms relating to the autonomic nervous system usually relate to loss of function or failure of the autonomic nervous system but autonomic hyperactivity can occasionally occur. Early symptoms can go unnoticed due to compensatory mechanisms (Donaghy 2009). Symptoms vary according to the system affected. For example, sympathetic adrenergic failure causes orthostatic hypotension (OH) and ejaculatory failure, while sympathetic cholinergic failure leads to loss of sweating. Parasympathetic failure causes dilated pupils, a fixed heart rate, urinary retention, an atonic large bowel and erectile dysfunction. With parasympathetic hyperactivity opposite features occur. In some disorders there may be a combination of effects, for example in neurally mediated syncope there is bradycardia caused by parasympathetic activity and hypotension resulting from withdrawal of sympathetic activity (Mathias 2003).

Some of the features of autonomic impairment are summarised below according to the system affected.

1.10.1 Syncope

Syncope is a transient loss of consciousness caused by a temporary reduction in cerebral blood flow. It can occur as a result of several disorders of the autonomic nervous system (Grubb 2005) as outlined below.

Orthostatic hypotension

Orthostatic hypotension (OH) is a decrease of at least 20 mm Hg in systolic blood pressure (SBP) or 10 mm Hg in diastolic blood pressure (DBP) on change of posture from lying to sitting or standing, or during the tilting phase of a head-up tilt (HUT) test (Mathias 2003; Lanier *et al.* 2011). During normal standing gravity causes blood to pool in the lower extremities. Baroreceptors are activated leading to an increase in

sympathetic activity with vasoconstriction and increased peripheral vascular resistance, thereby reducing the amount of blood pooling and maintained blood pressure (Lanier *et al.* 2011). Orthostatic hypotension occurs when the sympathetic activity is not sufficient to allow this to occur (Goldstein and Sharabi 2009). Symptoms of orthostatic hypotension occur when the perfusion pressure of organs, particularly the brain, are not sufficient. Symptoms include dizziness, cognitive deficits and loss of consciousness. Symptoms vary significantly among people with similar blood pressure drops. This may be related to differences in cerebral autoregulation (Zygmunt and Stanczyk 2010).

Neurocardiogenic Syncope

Activation of the sympathetic nervous system during standing results in increased contractility of the heart in an attempt to increase cardiac output. In neurocardiogenic syncope cardiac mechanoreceptors, which are normally activated during ventricular distension, are abnormally stimulated. This results in parasympathetic activation and sympathetic inhibition leading to reduced heart rate, reduced blood pressure and syncope. This can be diagnosed on HUT (Grubb 2005; Goldstein and Sharabi 2009), or in the setting of a typical clinical presentation.

Carotid Sinus Hypersensitivity (CSH)

Under normal circumstances stimulation of the carotid sinus results in reduced atrioventricular node conduction and reduced heart rate. In CSH this normal response is exaggerated. CSH is subdivided into 3 types-cardioinhibitory CSH, vasodepressor CSH and mixed CSH. Cardioinhibitory CSH is defined as asystole of 3 seconds or more. Vasodepressor CSH was defined as a drop of 50 mm Hg or more in systolic blood pressure and mixed CSH was a combination of both (Arthur and Kaye 2000).

Postural Orthostatic Tachycardia Syndrome (POTS)

POTS is a sustained increase in heart rate of at least 30 beats per minute (bpm) or to greater than 120 bpm on standing for 10 minutes. It is diagnosed using HUT. The pathogenesis of POTS involves impaired innervation of the peripheral vasculature or its inability to respond to the sympathetic nervous system. This leads to venous pooling in the extremities on standing, reduced venous return and a reflex tachycardia. It usually presents with palpitations, sweating, tremor and light-headedness on prolonged standing rather than syncope (Agarwal *et al.* 2007).

1.10.2 Cardiovascular System

Hypertension (HTN)

Increased sympathetic activity or reduced parasympathetic activity can lead to hypertension. Increased circulating noradrenaline from sympathetic nerve terminals has been found in patients with familial hypertension. The number and aptitude of sympathetic bursts is also higher in those with familial and white coat hypertension. Components of heart rate variability (HRV) that reflect parasympathetic activity are lower in those with hypertension (Mancia and Grassi 2014). Severe paroxysmal hypertension can occur in those with high spinal cord lesions due to uninhibited sympathetic activation (Mathias 2003).

Bradycardia

Bradycardia can occur in high spinal cord lesions. The afferent and vagal efferent components of the baroreflex are intact and the heart rate slows in an attempt to reduce blood pressure (Mathias 2003).

1.10.3 Genitourinary System

Bladder

During the storage phase of the micturition cycle the detrusor muscle relaxes to accommodate increasing volumes of urine and there is increased bladder outlet resistance. This is mediated by the sympathetic nervous system. In the voiding phase parasympathetic input causes detrusor contraction and reduces bladder outlet resistance (Ochodnicky *et al.* 2013). Loss of parasympathetic function causes an atonic bladder with urinary retention (Mathias 2003). Loss of sympathetic function would cause an increase in detrusor contraction leading to urinary frequency and incontinence.

Ejaculation

The sympathetic nervous system controls ejaculation by contracting the smooth muscle of the vas deferens, seminal vesicles and prostate (Snell 2010; Revenig *et al.* 2014). Loss of sympathetic activity therefore leads to failure of ejaculation.

Erectile Dysfunction

The parasympathetic nervous system causes relaxation of the erectile tissue to the penis and clitoris. Loss of parasympathetic activity therefore causes erectile dysfunction (Snell 2010).

1.10.4 Gastrointestinal Tract (GIT)

The parasympathetic nervous system increases GIT activity by promoting peristalsis, increasing blood flow and increasing intestinal secretion. The sympathetic nervous system has opposing effects (Winge *et al.* 2003). Common symptoms of autonomic impairment according to the organ involved are explained below.

Mouth

The parasympathetic nervous system supplies the salivary glands and causes an increase in salvation (Scully and Felix 2005) with dry mouth being a feature of reduced parasympathetic activity.

Oesophagus

In the oesophagus the parasympathetic nervous system provides motor innervation to the smooth muscle and secretomotor innervation to the glands. The sympathetic nervous system regulates blood vessel constriction, oesophageal sphincter contraction, relaxation of the muscular wall, and increases glandular and peristaltic activity (Kuo and Urma 2006). The main symptoms of autonomic dysfunction in the oesophagus are dysphasia and/or heartburn, which are due to impaired oesophageal mobility and gastro-oesophageal reflux (Bittinger *et al.* 1999).

Stomach

Activation of the sympathetic nervous system in the stomach causes constriction of the sphincters while the parasympathetic nervous system stimulates the smooth muscles for peristaltic movement and relaxes the sphincters (Browning and Travagli 2011). Therefore, to empty the pylorus, sympathetic stimulation must be inhibited and the parasympathetic system must be excited. Delayed gastric emptying or gastroparesis are common manifestations of autonomic dysfunction. Common symptoms are nausea, vomiting or feelings or fullness (Bittinger *et al.* 1999).

Bowel

The parasympathetic nervous system promotes peristalsis and controls the external anal sphincter. Loss of function causes constipation and incontinence (Paris *et al.* 2011).

1.10.5 Lungs

The sympathetic nervous system causes bronchodilation while the parasympathetic nervous system causes bronchoconstriction and gland secretion (Snell 2010). Stridor, snoring and nocturnal apnoea can occur in multiple systems atrophy (Mathias 2003).

1.10.6 Body Temperature

The sympathetic nervous system causes vasoconstriction of the blood vessels supplying the skin and increased secretion of sweat glands (Snell 2010). The inability to vasoconstrict, and therefore prevent heat loss, can result in hypothermia. Loss of sweating may prevent heat loss when exposed to high environmental temperatures and therefore cause a raised temperature (Mathias 2003).

1.11 Causes of Autonomic Impairment

In most incidences diseases related to the autonomic nervous system are sporadic, although genetic conditions such as familial dysautonomia do exist. Vasovagal syncope is often occupied by a family history especially in younger patients (Mathias 2003). Most of the nerves of the autonomic nervous system are made up of small myelinated or unmyelinated fibres. Conditions that cause autonomic impairment are likely those that affect these small fibres (McDougall and McLeod 1996).

Table 2 shows conditions that can result in autonomic dysfunction. In addition, medications such as levodopa or anti-hypertensives may unmask pre-existing autonomic deficits (Mathias 2003).

Table 2: Causes of Autonomic Impairment

Primary	Acute/subacute dysautonomias	Pure cholinergic dysautonomia Pure pandysautonomia Pandysautonomia with neurological features
	Chronic autonomic failure syndromes	Pure autonomic failure Multiple systems atrophy Autonomic failure with Parkinson's disease
Secondary	Congenital	Nerve growth factor deficiency
	Hereditary	Familial amyloid neuropathy Porphyria Hereditary sensory and autonomic neuropathies Familial dysautonomia
	Metabolic diseases	Diabetes mellitus Chronic renal failure Chronic liver failure Vitamin B12 deficiency
	Inflammatory	Bacterial-tetanus Viral-HIV Parasitic-Chagas' disease Prion-fatal familial insomnia
	Neoplasm	Brain tumours Paraneoplastic autonomic neuropathy Lambert-Eaton syndrome Primary amyloidosis
	Connective tissue disorders	Rheumatoid arthritis Systemic lupus erythematous Mixed connective tissue disease
	Surgery	Regional sympathetomy Vagotomy Organ transplant
	Trauma	Spinal cord transection
	Drugs	Alcohol

1.12 Tests of Autonomic Function

Many tests of autonomic function have been described however not all are suitable for routine clinical use (Donaghy 2009). Below is a description of some of the more practical to use tests.

1.12.1 Active Stand and Head Up Tilt Testing

Under normal circumstances, when an individual stands there is pooling of blood in the lower extremities. This activates baroreceptors and leads to increased sympathetic nervous system activity and peripheral vasoconstriction. A reduction of at least 20mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure indicates abnormal sympathetic function (Lanier *et al.* 2011). In an active stand test blood pressure and heart rate are recorded while lying down. The participant then stands up while continued measurements are taken. During a HUT, the participant remains lying on the tilt table which is then raised to between 60° and 80°. This removes the effect that the peripheral musculature has on venous return. The only differences in haemodynamic responses between the two tests is seen after the initial change in posture (Zygmunt and Stanczyk 2010).

1.12.2 Heart Rate Variability

Heart Rate Variability (HRV) is the variation in time between consecutive R waves in the cardiac cycle (RR interval). Heart rate is partially under the control of the autonomic nervous system. High sympathetic activity and low parasympathetic activity results in an increased heart rate, with the reverse causing a reduced heart rate. The variability in heart rate therefore provides an insight into the function of the autonomic nervous system (Acharya et al. 2006). HRV can be assessed using ambulatory monitoring and from this a number of calculations can be carried out. These measures can be split into those based on the time domain, frequency domain

or geometric measures (Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology 1996 [ESC 1996]).

Time Domain

1. SDNN

Normal-to-normal (NN) intervals are the RR intervals arising from sinus node depolarisation (Peltola 2007). The SDNN is the standard deviation (SD) of all the NN intervals (Acharya *et al.* 2006). It is an estimate of overall HRV (ESC 1996).

2. RMSSD

RMSSD is the root mean square of successive difference of intervals (Acharya *et al.* 2006). It is reflective of parasympathetic function (ESC 1996).

3. pNN50

This is the number of successive difference of intervals which differ by at least 50 milliseconds expressed as a total of the number of electrocardiography (ECG) cycles included in the analysis (Acharya *et al.* 2006). It is reflective of parasympathetic function (ESC 1996).

Geometric Measure- Triangular Index

The triangular index is a geometric measure of overall HRV. It is assessed from a RR interval frequency distribution diagram by dividing the number of all RR intervals by the maximum height of the density distribution (Kouidi *et al.* 2002).

Frequency Domain

Spectral analysis expresses heart rate as a function of frequency. It analyses the cyclical nature of changes in RR intervals. The frequency and magnitude of these changes are measured which allows separation of the data into different frequency components (Zygmunt and Stanczyk 2010).

1. Low Frequency (LF)

LF is contained in the range 0.04-0.15 Hertz (Hz) and is a measure of parasympathetic function.

2. High Frequency (HF)

HF is contained in the range 0.15-0.4 Hz and is a measure of parasympathetic function.

3. LF/HF ratio

The ratio reflects interactions of the sympathetic and parasympathetic nervous systems (ESC 1996; Zygmunt and Stanczyk 2010).

1.12.3 Blood Pressure Variability

Under normal physiological conditions changes in blood pressure occur as a regulatory response to environmental, emotional and behavioural stimuli. These short term blood pressure changes are mediated largely via changes in the sympathetic nervous system (Narkiewicz *et al.* 2002). Sustained increases in blood pressure variability (BPV) may reflect abnormalities in regulatory mechanisms such as impaired sympathetic or baroreflex function (Höcht 2013). Research has shown a direct relationship between higher sympathetic activity and greater BPV (Narkiewicz *et al.* 2002).

Several measures of BPV are available. The simplest measure is standard deviation, but this does not adequately reflect many important characteristics of BPV. It is largely impacted by night time fluctuations in blood pressure (Mena *et al.* 2017). It does not take into account the order in which blood pressure measurements are taken but rather examines their deviation from the mean (Pierdomenico *et al.* 2009). Average Real Variability (ARV) is an alternative measure of BPV and has been shown to be a better predictor of adverse outcomes (Mena *et al.* 2017).

1.12.4 Sweating

Lack of sweating can indicate impaired sympathetic function (Snell 2010). This can be tested by putting the patient's hand into a plastic bag to prevent evaporation and then warming it under a light. Ponzo red, which turns red on getting wet, can be dusted onto the hand (Donaghy 2009).

1.12.5 Valsalva Manoeuvre

The Valsalva manoeuvre is induced by forced expiration against a closed glottis. Normally an increase in intrathoracic pressure causes a transient rise in blood pressure and by activating baroreceptors, also results in a slight bradycardia (phase 1). As venous return reduces, blood pressure decreases with a compensatory rise in heart rate (phase 2). When the expiration is stopped and the intrathoracic pressure is released, continued sympathetic drive causes the blood pressure to rise above the initial level and as result of baroreceptor activation heart rate falls below the initial rate (final phase). In autonomic failure this increase in blood pressure and fall of heart rate below the basal level do not occur (Donaghy 2009; Zygmunt and Stanczyk 2010).

The Valsalva ratio can be calculated by dividing the longest RR interval in the final phase by the shortest RR interval in the second phase. This ratio is a measure of

parasympathetic function while changes in blood pressure reflect sympathetic function (Zygmunt and Stanczyk 2010).

1.12.6 Deep Breathing

Heart rate response to breathing is mediated by the vagal nerve and thus provides a test of parasympathetic function. The subject is asked to breathe at a rate of 6 breaths per minute, with each inspiration and expiration lasting for 5 seconds. The respiratory sinus arrhythmia amplitude is the difference between the heart rate at the end of expiration and the end of inspiration. Normal values decrease with age with a minimum of 7 bpm for those over sixty years and over (Novak 2011).

1.12.7 Isometric Handgrip Test

The isometric handgrip test evokes a sympathetic reflex with a resultant rise is heart rate, systolic and diastolic blood pressure. Participants are asked to squeeze a dynamometer to obtain their maximum voluntary contraction. They are then asked to maintain a grip at 30-40% of this level for 3 to 5 minutes. Blood pressure measurements are taken every minute (Khurana and Setty 1996; Nielsen and Mather 2015). In a normal test there should be a rise in diastolic blood pressure of at least 15mmHg (Zygmunt and Stanczyk 2010).

1.12.8 Cold Pressor Test

A hand or foot is placed in water at a temperature of between 1° and 5°C. Afferent pain and temperature neurons are activated leading to activation of the sympathetic nervous system. In normal subjects there should be a rise in heart rate and blood pressure (Wirch *et al.* 2006). Diastolic blood pressure should rise by a minimum of 15 mmHg (Zygmunt and Stanczyk 2010).

1.13 Treatment of Autonomic Impairment

Treatment of autonomic impairment largely depends on the predominant features present (McDougall and McLeod 1996) and is mainly targeted at treating the symptoms rather than the autonomic dysfunction itself (Kaufmann *et al.* 2015). Where an underlying condition has been identified this should also be treated if possible (McDougall and McLeod 1996).

1.13.1 Treatment of Orthostatic Hypotension

Treatment of OH include both pharmacological and non-pharmacological methods. Non-pharmacological methods include increasing fluid and salt intake to cause volume expansion and decreasing venous pooling through participation in physical activities (Figueroa *et al.* 2010). Although research is lacking for the benefit of their use, compression stocking are frequently used (Protheroe *et al.* 2011). Medications that are potentially contributing to hypotension, such as levodopa and alpha-blockers, should be eliminated where possible. Many patients require progression to pharmacological therapy (Kaufmann *et al.* 2015) as outlined below.

Midodrine

Midodrine is a vasoconstrictor and increases erect blood pressure. As it has a short duration of action, a three-times a day dosing regime is recommended. The main side effect is supine hypertension and therefore the last dose should be taken in the afternoon in order to prevent nocturnal hypertension (Figueroa *et al.* 2010).

Fludrocortisone

Fludrocortisone is a synthetic mineralocorticoid that is of benefit in the treatment of orthostatic hypotension due to its ability to volume expand. It also increases vascular alpha-adrenoreceptor sensitivity. As it causes fluid retention it is contraindicated in

congestive cardiac failure and chronic renal failure. It can also cause hypokalaemia and supine hypertension (Figueroa *et al.* 2010).

Pyridostigmine

Pyridostigmine is an inhibitor of acetylcholinesterase that enhances ganglionic transmission in the sympathetic nervous system. It has been shown to increase orthostatic blood pressure and reduce orthostatic symptoms without worsening supine hypertension (Singer *et al.* 2006).

Droxidopa

Droxidopa is a synthetic amino acid that is converted into noradrenaline. It was approved by the American Food and Drug Administration in 2014 for the short-term treatment of neurogenic orthostatic hypotension. It has been shown to reduce symptoms of orthostatic hypotension and the impact that it has on daily life. The most common side effect reported is headache, although supine hypertension is another potential complication (Kaufmann *et al.* 2015).

1.13.2 Treatment of GIT Symptoms

Delayed gastric emptying may respond to prokinetic agents such as the dopamine antagonists metoclopramide and domperidone. Erythromycin, which is an agonist of the motilin receptor, can also be used as a prokinetic agent.

Constipation should be treated with adequate hydration, high fibre diet and the use of laxatives.

High fibre diet and bulking agents may also help with faecal incontinence (McDougall and McLeod 1996).

1.13.3 Treatment of Genitourinary Symptoms

Urinary Retention

Doxazosin is an alpha-adrenergic receptor blocker which may help reduce urinary retention by reducing bladder outlet pressure, but many patients will ultimately require catheterisation (McDougall and McLeod 1996; Duby *et al.* 2004). Doxazocin does have significant side effects and is often poorly tolerated by older adults due to its effects on blocking peripheral alpha-1 adrenoreceptors in vascular smooth muscle, which can cause or worsen orthostatic hypotension (Fulton *et al.* 1995).

Erectile Dysfunction

Medications that can contribute to sexual dysfunction such as beta-adrenoreceptor blocking agents and spironolactone should first be discontinued. Psychological factors should be addressed. A trial of a phosphodiesterase inhibitor, for example sildenafil, can be given if there are no contraindications (Duby *et al.* 2004)

1.14 Summary of Autonomic Nervous System

The autonomic nervous system is a complex system involved in maintaining normal body function. Autonomic impairment can have multiple potential causes. The clinical presentation is non-specific and can depend on the component of the autonomic nervous system affected. Treatment is largely targeted at symptom relief.

1.15 Chapter Conclusion

Chapter 1 has provided an overview of both the autonomic nervous system and delirium. Chapter 2 will now discuss the rationale for looking for an association between the two conditions and provide a summary of the current available literature.

Chapter 2: Rationale for Looking for an Association Between Delirium and Autonomic Impairment

2.0 Prologue to Chapter

Chapter 2 outlines the reasons for looking for an association between delirium and autonomic impairment. It examines potential links between the two conditions including altered cerebral perfusion, endothelial dysfunction and the role of acetylcholine. This chapter also details a literature review carried out to look for any previous studies that have investigated for a potential relationship.

2.1 Cerebral Perfusion

Adequate cerebral perfusion is required to provide sufficient oxygenation of cerebral cells and to prevent cerebral dysfunction (Ali *et al.* 2011). Measures of oxygenation and oxidative stress have been found to be worse in patients with delirium than in controls (Seaman *et al.* 2006). Other research suggests that delirium may be related to reduced cerebral perfusion (Ali *et al.* 2011). During cardiac surgery patients with higher systemic blood pressure, and therefore higher cerebral blood flow, have been shown to be less likely to develop post-operative delirium than those with lower perfusion pressures (Siepe *et al.* 2011). Similar results were shown for patients who had cerebral perfusion pressures measured during lung transplant surgery (Smith *et al.* 2016). Studies based on neuroimaging have shown reduced cerebral blood flow in patients with delirium compared to after delirium resolution (Yokota *et al.* 2003; Fong *et al.* 2006). Cerebral blood flow declines with age (Donaghy 2009), which could potentially make older people more susceptible to delirium than their younger counterparts.

Cerebral perfusion pressure is the difference between arterial and venous pressure in the brain. According to Poiseuielle's law cerebral blood flow is directly related to cerebral perfusion pressure, blood viscosity and the length of the blood vessel

(assumed to be constant). It is inversely related to the radius to the fourth power. Flow is calculated by using the following formula:

Flow=$(8nL)/r^4$, where n=blood viscosity, L=length of vessel, r=radius of vessel.

Thus, small changes in the radius of a blood vessel can have a significant effect on cerebral blood flow.

Cerebral autoregulation is the process by which the brain maintains a constant blood flow despite changes in perfusion pressure (Cipolla 2009). It does this through altering the blood vessel radius and therefore the resistance level of the vessel (Hu *et al.* 2008; Cipolla 2009). When cerebral perfusion pressure is in the range of 60 to 160mmHg, cerebral blood flow normally occurs at a rate of 50ml per 100g of brain tissue per minute. When cerebral perfusion pressure is outside of this range cerebral autoregulation is lost. At higher pressures cerebral perfusion pressure becomes dependent on mean arterial pressure in a linear fashion. At lower cerebral perfusion pressures there is initially a compensatory increase in oxygen extraction to maintain cerebral metabolic needs. When perfusion pressure falls sufficiently to prevent this, signs of hypoperfusion occur, such as altered mental status and dizziness (Cipolla 2009). Thus patients with autonomic impairment and postural hypotension could have drops in their perfusion pressure at a level sufficient to fall below the autoregulatory range. Previous research has shown that patients with known autonomic failure have lower cerebral blood flow during Head-Up Tilt testing than controls (Novak *et al.* 1998).

Cerebral autoregulation is affected by a number of factors including the autonomic nervous system and carbon dioxide levels. Sympathetic nervous system activation causes vasoconstriction and reduced cerebral blood flow while activation of the parasympathetic nervous system causes vasodilation and increased cerebral blood

flow (Tameem and Krovvidi 2013). Cerebral autoregulation is disrupted in cerebral small vessel ischaemia, hypertension and diabetes (Guo *et al.* 2015).

I therefore hypothesise that autonomic dysfunction could be associated with the development of delirium by causing sudden reductions in systemic blood pressure, and therefore reduced cerebral perfusion, and/or by disrupting cerebral autoregulation.

2.2 Endothelial Dysfunction

The endothelium is a single layer of cells that lines the lumen of blood vessels. It plays a role in the regulation of vascular tone, thrombosis and inflammation. The endothelium leads to vasodilation through the release of a number of vasoactive substances, the main one being nitric oxide. These substances lead to vasodilation through their interaction with the smooth muscle in the blood vessel wall. Cholinergic nerve endings of the autonomic nervous system are found in the endothelium and are coupled with the formation of nitric oxide, although the autonomic nervous system can regulate vasodilation even if nitric oxide is blocked. Endothelial dysfunction and autonomic impairment co-exist in several cardiovascular disease processes (Amiya *et al.* 2014).

In a study investigating an association between endothelial dysfunction and delirium or coma among critically ill ICU patients, participants with endothelial dysfunction had less delirium or coma free days and longer durations of delirium. This suggests that endothelial dysfunction could play a role in the development of delirium (Hughes *et al.* 2013).

Given the role of the autonomic nervous system in endothelial function, further investigation into an association between delirium and the autonomic nervous system is justified.

2.3 Role of Acetylcholine

Acetylcholine is one of the two main neurotransmitters involved in the autonomic nervous system (McCorry 2007). It is also involved in attention and memory and a deficiency of acetylcholine is therefore thought to be involved in the pathophysiology of delirium (Ali *et al.* 2011). Administration of anti-cholinergic agents can induce delirium (Flacker and Lipsitz 1999) and increased anticholinergic activity has been shown to be associated with the development of delirium (Tune *et al.* 1981; Golinger and Tune 1987). Given the role of acetylcholine in the autonomic nervous system, further investigation to establish if there is an association between autonomic impairment and delirium is warranted.

2.4 Review of the Available Literature

A search of Pubmed, Embase, Cochrane Library, CINAHL and PsycINFO was carried out using PRISMA guidelines. Studies published before January 2017 were included. Titles and abstracts were searched using the search terms delirium, delirious, acute confusion, acute confusional state, encephalopathy, organic brain syndrome, brain dysfunction and brain failure which were cross-referenced with the terms autonomic nervous system, sympathetic nervous system, parasympathetic nervous system, autonomic function, sympathetic function, parasympathetic function, autonomic failure, autonomic impairment, autonomic dysfunction, autonomic dysreflexia,

dysautonomia, heart rate variability, blood pressure variability, postural hypotension and orthostatic hypotension.

Studies were included if they compared autonomic function in delirious participants to non-delirious controls, were clinical studies with human participants and had text available in English.

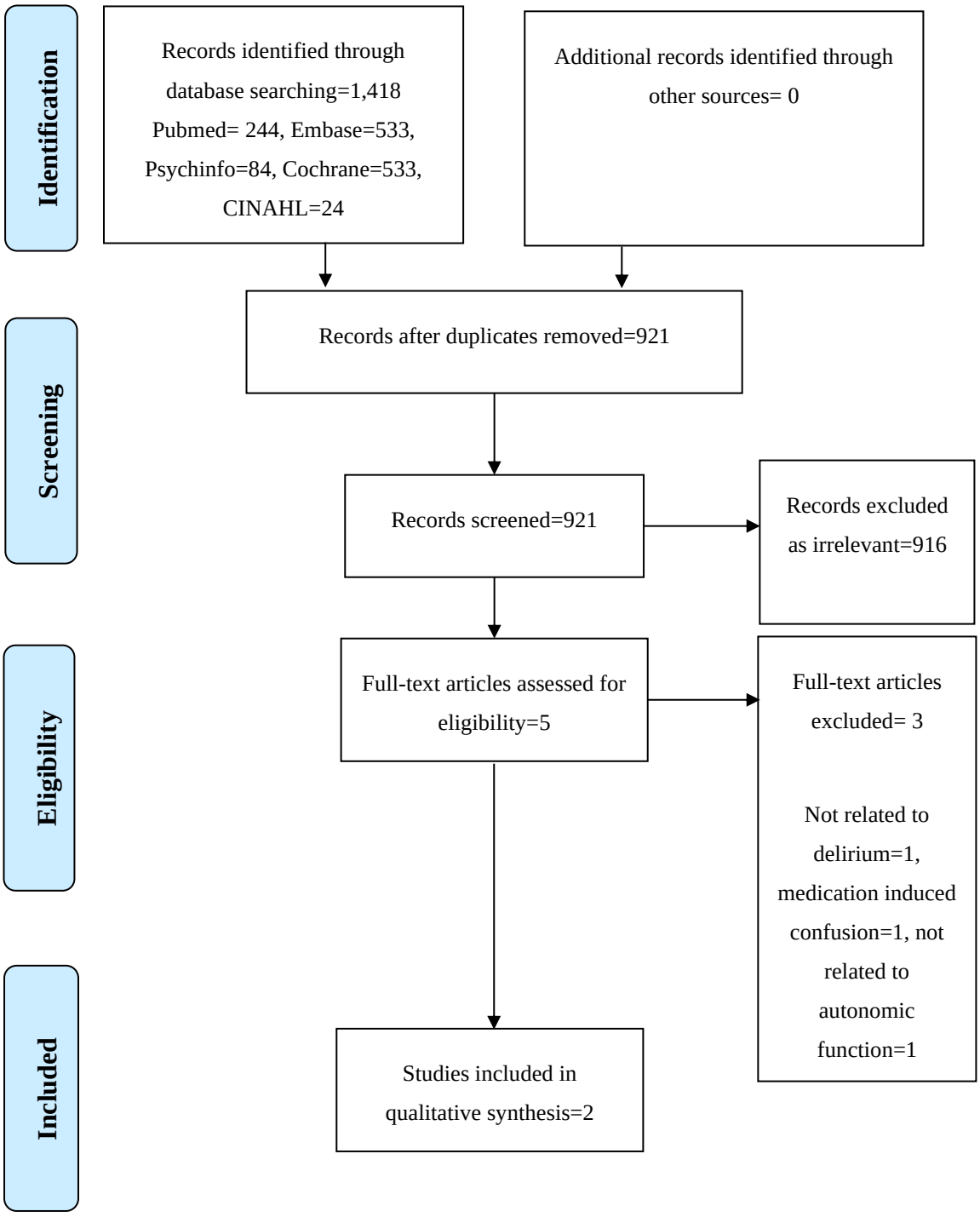
Studies were excluded if they investigated confusion due to alcohol, drugs, traumatic brain injury, hypoxic brain injury or hepatic encephalopathy as the underlying pathophysiology may be different in these conditions.

Of the 921 studies retrieved following removal of duplications, 916 were not related to the autonomic nervous system and delirium. Of the remaining 5 studies, 3 did not meet inclusion criteria leaving just 2 studies that investigated the relationship between autonomic impairment and delirium. The reference list of these studies was searched and no additional studies were identified. A summary of the study selection process is shown in Figure 5.

One of the two studies found, Bolton et al (Bolton *et al.* 2007), investigated the relationship between various neurological disorders in the ICU and the autonomic nervous system. Sympathetic nervous system function was investigated using sympathetic skin response and parasympathetic function was investigated using heart rate variability (HRV). Of the patients recruited, only two patients had delirium. The remaining participants had neurological conditions unrelated to delirium. They reported an abnormally fixed R-R interval and absent sympathetic skin response in the two patients with sepsis related delirium. The very small number of two delirious patients and lack of control group of non-delirious patients, limits the interpretation of these results.

The second study retrieved, Zaal et al (Zaal *et al.* 2014), compared HRV in ICU patients with and without delirium. It was a prospective observational study. Participants from 30 to 80 years of age were recruited. Delirium screening was carried out using the Dutch version of the CAM-ICU. HRV was calculated using spectrum analysis of data collected over a 15 minute period. 13 patients with delirium and 12 patients without delirium were included. Patients with delirium were older with a mean age of 67 compared to 57 years in the non-delirious group. There were more women in the delirium group (6 compared to 1). 69% of delirious patients and 50% of the controls were mechanically ventilated during the HRV recordings. Zaal et al reported no difference in HRV between the two groups. It is however worth noting the differences in age and gender between the two groups, both of which can impact on HRV (Zhang 2007). HRV has been shown to be lost during critical illness making patients in both groups susceptible to abnormalities in HRV (Buchman *et al.* 2002). In addition, HRV is altered during mechanical ventilation (Kasaoka *et al.* 2010). Given that over half of the patients in this study were mechanically ventilated, the generalisability of the results to all patients with delirium is limited. This study remains important as it is the only study found that investigates a possible relationship between autonomic impairment and delirium.

Figure 5: PRISMA 2009 Flow Diagram



2.5 Conclusion

As outlined above there are several potential mechanisms that would support an association between autonomic impairment and delirium. Only one study has investigated this potential relationship and although no association was identified, the study was limited by the population studied and may not reflect the population of delirium patients as a whole. In addition, it only investigated HRV, a single test of autonomic function. Further investigation is therefore justified. This should take into consideration patients outside of the ICU setting and include further tests of autonomic function.

Chapter 3: Study Design and Methodology

3.0 Prologue to Chapter

This chapter outlines the study undertaken as part of this thesis to investigate for evidence of an association between autonomic impairment and delirium. It describes the study design, the aims and hypothesis of the study as well as detailing the study assessment tools used.

3.1 Study Overview

This study is an exploratory study to evaluate for a relationship between delirium and autonomic impairment. It is a prospective case control study with the cases being defined as participants who fulfilled diagnostic criteria for delirium and controls defined as participants who did not meet the diagnostic criterion. The diagnostic criteria are outlined in Section 3.10.2.

3.2 Hypothesis of the Study

The primary hypothesis of this study is that patients with delirium are more likely to have demonstrable autonomic dysfunction than patients without delirium, taking confounding factors such as age, severity of illness and medical comorbidities into account.

Direct measurement of autonomic dysfunction is difficult, however there are well accepted surrogate measures and these include blood pressure variability, heart rate variability, abnormal diurnal blood pressure response and orthostatic blood pressure changes (as measured by tilt table testing). I hypothesise that individuals who developed delirium will demonstrate increased blood pressure variability, reduced

heart rate variability, abnormal diurnal blood pressure profiles and a greater tendency to orthostatic blood pressure drops.

3.3 Study Objectives

The primary objective of the study is to assess if there is a relationship between delirium and autonomic dysfunction.

If such a relationship is found, then the secondary objectives of the study are:

1. To look for a relationship between the severity of delirium and severity of autonomic dysfunction
2. To establish if autonomic function varies with delirium subtype

3.4 Recruitment

Patients aged 65 years or older who were under the care of a consultant geriatrician were considered for inclusion. This was required in order to ensure that participants with previously undiagnosed cognitive impairment, that were detected during the course of the study, could be followed up on an ongoing basis. The age criterion was applied to help ensure equal age distribution between the two groups as the incidence of delirium increases with age (Kukreja *et al.* 2015).

All participants were recruited during an inpatient stay in University Hospital Limerick.

A convenience sample of patients were selected on days in which the investigator was available to recruit participants. The geriatric teams identified potential participants who were medically appropriate for inclusion and did not meet any of the exclusion criteria. These individuals were made known to the investigator, who then invited them to participate. The inclusion and exclusion criteria used are shown in Table 3.

Table 3: Study Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• An inpatient at time of recruitment • Aged 65 years or older • Under the care of a consultant geriatrician	• Medically unfit for assessment or requiring intensive care admission • Delirium due to alcohol or substance withdrawal where the underlying pathophysiology of delirium may be different • Co-morbid, uncontrolled moderate or severe depression as this may interfere with delirium assessments • Excessive drowsiness or coma • Severe expressive or receptive dysphasia as this may affect the ability to complete assessments • Co-morbid psychotic disorder • Patients deemed likely to require end of life treatment as assessed by a consultant geriatrician • Acute stroke or acute transient ischaemic attack as cerebral autoregulation may be disrupted • Intracerebral tumour as cerebral autoregulation may be disrupted • Acute myocardial infarction as heart rate variability may be altered • Inability to comply with Head-Up Tilt testing or ambulatory monitor testing • Inability to attend follow up

Table 3 shows the inclusion and exclusion criteria for the study. Participants had to meet all the inclusion criteria and were excluded if they meet one or more of the exclusion criteria. There was no exclusion of participants based on medication use.

3.5 Sample Size

A systematic review of this topic was completed and there was no available literature on which to base a sample size calculation. As outlined in Chapter 2 one study was identified (Irene J. Zaal *et al.* 2014) that compared autonomic function in participants with delirium to normal controls. This was however carried out in an ICU population, which is different to the population of general older inpatients included in this study. Zaal et al used a single measure of autonomic function, short term heart rate variability. The present study uses different measures of autonomic function which are routinely collected during tilt table testing and 24-hour blood pressure and holter monitoring in our syncope unit. A formal sample size calculation based on the previous study was therefore not appropriate. As this was however the only available study, I did include a similar sample size in my study. I therefore aimed to carry out autonomic function testing on 25 participants. Given that the population included are older adults with comorbidities, I anticipated that not all participants initially recruited would attend for follow up. Recruitment was therefore continued until a sufficient number of participants had attended follow-up.

As the sample size was small it was important to choose autonomic function tests with good reproducibility and low variability in results. Cardiovascular responses to HUT in a cohort of healthy, older adults were similar when carried out at baseline and six weeks (Youde et al. 2003). A previous retrospective review of patients attending our syncope unit showed that sit-to-stand blood pressure testing was not sensitive for the diagnosis of orthostatic hypotension as compared to HUT (Cooke *et al.* 2009). Heart rate variability measured over 24 hours is more reproducible than short term recordings (Morrin et al. 2017). 24-hour ambulatory systolic blood pressure monitoring is reproducible to within 2.8-3.8mmHg over four separate occasions (Morrin et al. 2017).

3.6 Case Allocation

Participants were assigned to either the case or control group following an assessment for delirium. Participants who meet all four DSM-IV criteria for delirium (see Section 3.10.2) were recruited into the case/delirium group and those who did not meet all four diagnostic criteria were recruited to the control group. Thus participants with some, but not all features of delirium (subsyndromal delirium) may have been included in the control group. Use of the Delirium Rating Scale-Revised 1998 (DRS-R98) allowed the impact of the severity of subsyndromal delirium and delirium to be evaluated.

3.7 Consent Process and Ethical Considerations

Consent was obtained for all participants. Where a participant had capacity to provide consent, it was obtained from them. Where a participant did not have capacity to provide consent, in accordance with the Declaration of Helsinki, assent was obtained from their caregiver. If capacity returned during the study, informed consent was obtained from the participant. To avoid subjecting participants to repeated capacity tests, repeat testing was only carried out if capacity was suspected to have returned.

Written consent was obtained where possible. Where a care-giver was unable to attend in person to sign an assent form, verbal assent over the phone was obtained. The consent form for participants can be found in Appendix A and the consent form for family members can be found in Appendix B.

Participants or their family member received a written information leaflet (Appendix C) outlined the study objective, methods, risks and benefits. They were informed that they were under no obligation to participate in the study, they could withdraw consent at any point without their care being impacted by not participating in this study.

Participants consented to the results of their study assessments being recorded in their medical notes and to be given to their primary consultant. This ensured that any abnormalities detected received further evaluation and treatment as required.

Ethical approval for this study was received from University Hospital Limerick's Research and Ethics Committee.

3.8 Sequence of Events Following Recruitment and Consent

The following demographic details were recorded at the initial assessment:

- Date of birth
- Date of admission
- Date of assessment
- Admission diagnosis
- Past medical history
- Medications

3.8.1 Cognitive Assessment

An evaluation for the presence of delirium was carried out using the Delirium Rating Scale-Revised 1998 (DRS-R98) and a diagnosis of delirium made using Diagnostic and Statistical Manual of Mental Disorders 4th Edition criteria (DSM-IV). DRS-R98 was also used to assess delirium severity. The Delirium Motor Subtyping Scale 4 (DMSS-4) was used to classify delirium into subtypes (hypoactive, hyperactive, mixed or no subtype). A description of these assessments can be found later in this chapter.

I carried out all of these assessments and completed appropriate training prior to the study commencing. Training was carried out by a psychiatrist who was experienced in the use of these tools in the research setting.

3.8.2 Confounding Factors

A number of assessments were carried out in order to identify major confounding factors that might impact on the study outcomes. The Eight Item Interview to Differentiate Aging and Dementia (AD8) was carried out to look for pre-existing cognitive impairment. The severity of acute illness was classified based on the Acute Physiology and Chronic Health Evaluation II (APACHE II) scale. A 32 item Frailty Index (FI) (Appendix H), based on the Rockwood Frailty Index, was used to evaluate for the presence of frailty. The Modified Barthel Index was used to establish baseline functional status and the Charlson Comorbity Index was used to objectively measure comorbid illness. A description of these assessments can be found later in this chapter.

3.8.3 Discharge

Participants were discharged by their treating team when clinically appropriate. This was independent of study participation.

3.8.4 Outpatient Follow-up

Sepsis, acute illness and volume depletion would be likely to interfere with the measurement of autonomic function in the setting of an acute hospital admission. Therefore, autonomic function testing took place following discharge, at a time when the participant was free of an acute illness that could impact on the results.

A Head-Up Tilt test took place to look for orthostatic hypotension or orthostatic hypertension. Continuous blood pressure and heart rate monitoring took place during HUT to evaluate baroreflex sensitivity (BRS) and allow calculation of the

baroreceptor effective index (BEI), which is a measure of BRS. A 24-hour ambulatory blood pressure monitor (ABPM) was completed to evaluate blood pressure variability (BPV) and the presence or absence of night-time reductions in blood pressure. A 24-hour holter monitor was carried out to look for heart rate variability (HRV).

A description of these assessments can be found later in this chapter.

HUT and ambulatory monitoring were carried out by nurse specialists whose routine clinical work involves administering these tests. I interpreted all test results, the process of which is part of my clinical practice.

A schema of the study design is shown in Figure 6.

Figure 6: Study Overview

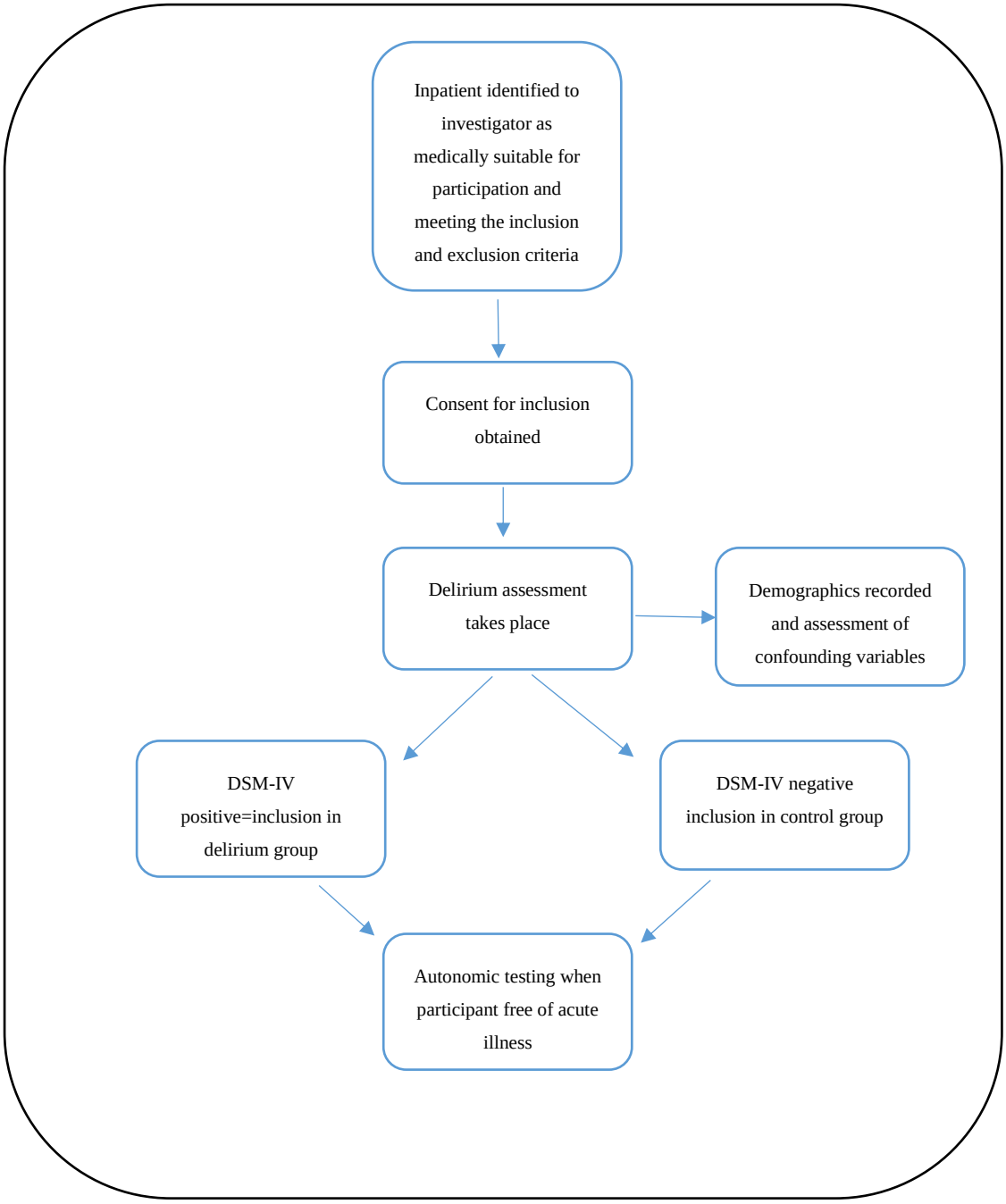


Figure 6 shows an overview of the study process from participant recruitment to completion of autonomic function testing. Participants with some, but not all features of delirium (subsyndromal delirium), who therefore did not meet the DSM-IV criteria for delirium, were included in the control group. Use of the Delirium Rating Scale-Revised 1998 (DRS-R98) allowed the impact of the severity of subsyndromal delirium and delirium to be evaluated.

3.9 Data Management

A pseudonymisation process was used in this study. Participants were assigned a study identification number following consent. A paper file was kept which contained the participant's details and their assigned study identification number. This was kept in a locked filing cabinet, in a locked office in University Hospital Limerick. The study identification number was recorded on all assessments carried out.

Assessments for delirium and confounding variables were recorded in paper format. Paper reports were generated for the autonomic function tests. All paper documents were kept in a locked cabinet, in a locked office in University Hospital Limerick.

The onymous, original electronic reports for the autonomic function tests remained on the hospital's secure, encrypted servers for use in clinical practice.

Data was entered into Microsoft Excel and IBM Statistical Package for Social Sciences (SPSS) for analysis. The study identification number was used to label participants in these databases.

3.10 Description of Study Assessments

3.10.1 Delirium Rating Scale-Revised 1998 (DRS-R98)

The DRS-R98 (Appendix D) is designed for the broad assessment of delirium. It can be used as both a diagnostic test for delirium and a valid and reliable rating scale for delirium severity. It is a 16-item scale with a 13-item severity section, which can be scored separately to the 3-item diagnostic section. The sum of the two sections allows calculation of the total score.

Each item on the severity scale is rated 0 (absent/normal) to 3 (severe impairment). Severity scale scores range from 0 to 39, with higher scores indicating more severe delirium. There are three diagnostic items (rated 0-2 or 0-3). The total scale score ranges from 0 to 46 (Trzepacz *et al.* 2001). A diagnosis of delirium using DRS-R98 is made when the total score is greater than or equal to 18 in patients with co-morbid dementia or greater than or equal to 15 in patients without co-morbid dementia. Scores between 8 and 15 are considered subsyndromal delirium.

DRS-R98 assessments are carried out using all available sources of information such as medical notes, patient assessment and collateral history from staff and family.

The DRS-R98 has high inter- reliability, sensitivity and specificity for detecting and distinguishing delirium from mixed neuropsychiatric conditions such as dementia, depression and schizophrenia (Trzepacz *et al.* 2001).

In this study the DRS-R98 was used to make an assessment for the presence of delirium and to rate the severity of delirium. The inattention section was evaluated using patient interaction and the Months Backwards test. This is a validated test to detect inattention in delirious patients (O'Regan *et al.* 2014). Short term memory was assessed by requesting the participant to recall three words. Clock drawing and copying intersecting pentagons was used to inform visuospatial ability scores (Trzepacz *et al.* 2001).

3.10.2 Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DSM-IV)

The presence of delirium was confirmed if the participant fulfilled the criteria for delirium according to DSM-IV. The presence of all four criteria is required for a diagnosis to be made. Assessment for fulfilment of these criteria was based on all

available data including admission notes, geriatric assessment, DRS-R98 assessment and collateral history from family and/or hospital staff involved in the care of the patient.

The diagnostic criteria are shown in the Figure 7 below.

Figure 7: DSM-IV Criteria for Delirium

A. A disturbance of consciousness (i.e. reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.

B. A change in cognition (such a memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia.

C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

D. There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

The presence of all four criteria above are required to confirm the diagnosis of delirium.

3.10.3 Eight-Item Questionnaire to Differentiate Aging and Dementia (AD8)

The AD8 (Appendix E) is a validated informant questionnaire that is sensitive for detecting both mild cognitive impairment and various types of dementia including

Alzheimer's Disease, vascular dementia, Lewy Body dementia and frontotemporal dementia (Razavi *et al.* 2014). The AD8 is a formal, validated mechanism for obtained a collateral history from a family member. In this study the AD8 was used as part of the initial evaluation during the delirious episode in order to allow underlying cognitive impairment to be controlled for at a time with other evaluations such as the Montreal Cognitive Assessment (MoCA) would not be reliable. Compared to an alternative collateral questionnaire, the IQCODE, the AD8 has been shown to be equal in the detection of dementia but superior in detection of mild cognitive impairment (Razavi *et al.* 2014). The questionnaire was not carried out for participants who already had an established diagnosis of dementia.

3.10.4 Abbreviated Delirium Motor Subtyping Scale (DMSS-4)

The DMSS-4 was used to classify delirium into motor subtypes (hypoactive, hyperactive, mixed or none). It has a high concordance with the original, full DMSS (Meagher *et al.* 2014). In this study the DRS-R98 was used to inform classification of the motor subtype.

3.10.5 Charlson Comorbidity Index

Standardized documentation of comorbidities took place using the Charlson Co-Morbidity Index (Appendix F). It is a validated tool used to measure burden of disease and one-year mortality risk. The index consists of 17 comorbidities (Roffman *et al.* 2016). Extra points are added for older age groups, with one point added for those aged 50-59 years, 2 points added for those aged 60-69 years, 3 points for added for those aged 70-79 years and 4 points added for those aged 80 or above.

3.10.6 Acute Physiology and Chronic Health Evaluation II (APACE-II)

Illness severity was rated using the internationally accepted APACE-II scoring system (Appendix G). It is a twelve-item scoring system, with different weights used for

different variables. The maximum score is 71, with a higher score being associated with greater disease severity and increased risk of death. While it has been validated mainly in ICU cohorts, it is widely researched and used to document severity of illness in the literature (Bouch and Thompson 2008). As an arterial blood gas is not routinely carried out in all patients, serum bicarbonate was substituted for arterial pH in participants with normal oxygenation (Wagner and Draper 1984).

3.10.7 Frailty Index (FI)

A Frailty Index measures frailty based on the number of health deficits that a person has accumulated. These deficits can take a wide range of forms including symptoms, diseases, disabilities, psychosocial factors or cognitive impairments. A minimum of 30 items is required to make the frailty index valid. In order to be considered a deficit for a frailty index an item must meet 5 criteria.

1. Must be associated with health status
2. The prevalence of the deficit should in general increase with age
3. Although the prevalence should increase with age it must not saturate too early
4. The deficits as a group must cover a wide range of systems
5. If a frailty index is used on the same person more than once the same list should be used each time

The FI is calculated by dividing the total number of deficits a person has by the total number on the list (Searle *et al.* 2008). A FI of less than 0.08 is considered normal, FI of greater than 0.25 is considered frail and scores between these values are considered pre-frail.

The frailty index used in this study can be found in Appendix H. It was measured based on the health deficits present at admission.

3.10.8 Barthel Index

The Barthel Index (Appendix I) is a measure of functional status. It records a person's ability to carry out ten common activities of daily living. The maximum total score is 100. A lower score indicates higher levels of dependency (Quinn *et al.* 2011).

3.10.9 Head-Up Tilt (HUT)

Head-up tilt testing is an investigation routinely used in the investigation of autonomic dysfunction. Patients lie supine on a bed for a period of three to five minutes. Supine blood pressure is recorded once blood pressure readings are stable. The tilt-table is then tilted to 70° with continuous beat-to-beat heart rate and blood pressure monitoring. This continues for 3 minutes. If blood pressure falls the lowest blood pressure reached is recorded. If blood pressure rises the steady state blood pressure is recorded.

Orthostatic hypotension is defined as a drop in systolic blood pressure of at least 20mmHg or a drop in diastolic blood pressure of at least 10mmHg. Orthostatic hypertension is defined as a rise in blood pressure by the same values.

In this study HUT testing was carried out using CNSystems Task Force® Monitor. Testing took place on an outpatient basis when the participant was free of acute illness.

3.10.10 Baroreceptor Sensitivity (BRS)

The baroreceptor system plays an important role in the short-term blood pressure management and helps to prevent wide fluctuations in pressure. Changes in blood pressure are detected by stretch receptors in the carotid sinus and aortic arch. A reduction in blood pressure leads to increased sympathetic activity and reduced parasympathetic activity. Physiologically the result is increased heart rate, peripheral vascular resistance, cardiac contractility and venous return, thus increasing systemic

blood pressure. An increase in blood pressure detected by stretch receptors has the opposite effect (La Rovere *et al.* 2008).

BRS testing took place at the same time as the HUT. BRS was measured using the Baroreflex Effectiveness Index (BEI). This is carried out by analysing beat-to-beat fluctuations in blood pressure and the corresponding changes in heart rate (La Rovere *et al.* 2008) or RR interval. The RR interval is the time between two consecutive R waves in the cardiac cycle.

In this study continuous non-invasive blood pressure and heart rate monitoring were carried out using the Task Force ® Monitor from CNSystems. The build-in software identifies three or more consecutive beats where there is a progressive increase or decrease in blood pressure. It then looks at the changes in RR interval that accompany this. The BEI is the proportion of changes in blood pressure that are accompanied by an appropriate change in RR interval. This can be subdivided into increases in blood pressure accompanied by increases in RR interval (BEI-Up) and decreases in blood pressure accompanied be decreases in RR interval (BEI-Down).

Participants were asked to lie supine for a period of three minutes with continuous monitoring. They were then placed in a 70° tilted position and monitoring was continued for a further three minutes. BEI was analysed separately for the supine and tilted periods.

3.10.11 Blood Pressure Variability (BPV)

As discussed in Section 1.12.3, blood pressure variability is a marker of sympathetic function. As Average Real Variability (ARV) is a better predictor of adverse outcomes than standard deviation (Mena *et al.* 2017), it was chosen as the measure of blood pressure variability in this study.

24-hour blood pressure monitoring (ABPM) took place when the participant was free of an acute illness that could impact on the results. Blood pressure was recorded every 15 minutes during the day and every 30 minutes at night. Individual blood pressure readings were entered into a spreadsheet (Microsoft Excel 2013). From these readings ARV was calculated using the formula:

$$ARV = \frac{1}{n-1}\sum_{i=1}^{n-1}\left|BP_{i+1} - BP_i\right|$$

3.10.12 Diurnal Blood Pressure Variability

Under normal circumstances there is a reduction in blood pressure at night by 10-20% (Calhoun and Harding 2010). This is associated with a reduction in sympathetic drive. The normal increase in blood pressure on awaking reflects activation of the sympathetic nervous system. Loss of night-time dipping in blood pressure reflects abnormally high levels of sympathetic activity (Sherwood *et al.*) and has been shown to correlate to worsening cardiovascular outcomes (Tsioufis *et al.* 2011).

In this study, diurnal blood pressure changes were measured using the same 24-hour ambulatory monitor used to calculate ARV. Average daytime and night-time blood pressure readings were automatically calculated by the device. The percentage difference between the day and night-time measurements was calculated and used to define dipping status. Dipping status was classified as follows:

Normal dipper: nocturnal blood pressure reduced by 10-20%
Extreme dipper: nocturnal blood pressure reduced by greater than 20%
Reverse dipper: nocturnal increase in blood pressure of at least 20%
Non-dippers: nocturnal reduction in blood pressure of between 0% and 10%

3.10.13 Heart Rate Variability (HRV)

Heart rate is regulated by the interaction of the sympathetic and parasympathetic nervous systems. Activation of the parasympathetic system causes hyperpolarisation of cardiac pacemaker cells which reduces the rate of depolarisation and in turn reduces heart rate. Sympathetic activation has the opposite effect. HRV is a non-invasive measurement of autonomic nervous system function. In a normally functioning system there will be physiological variations in heart rate (Sztajzel 2004).

HRV was recorded when the participant was free of acute illness using a 24-hour holter monitor. The data recorded was imported into Kubios HRV Standard which is a software package designed for calculating HRV (Tarvainen *et al.* 2014). Tracings were reviewed and non-sinus beats removed prior to analysis. The software then calculated HRV.

As outlined in Section 1.12.2, there are various possible measures of HRV. Time domain measures use mathematical calculations based on the intervals between successive sinus beats. Two different time domain measures are used in this study, SDNN and RMSSD. SDNN is an estimate of overall HRV and RMSSD is reflective of parasympathetic function (ESC 1996).

An alternative method of calculating HRV is using spectral analysis which expresses heart rate as a function of frequency. Low Frequency (LF) components are contained in the range of 0.04-0.15 Hertz (Hz) and are measure of sympathetic activity. High Frequency (HF) components are in the range of 0.15-0.4 Hz and are a measure of parasympathetic activity. The LF/HF ratio reflects interactions of the sympathetic and parasympathetic nervous systems (ESC 1996; Zygmunt and Stanczyk 2010).

Various computerised algorithms are available for spectral analysis, the Fast Fourier Transform was the algorithm used by the Kubios HRV Standard software to calculate HRV.

3.11 Statistical Analysis

IBM SPSS Statistics 25 was used for statistical analysis.

The total number of blood pressure reducing agents each participant was prescribed was computed and included alpha-receptor blocking agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-receptor blocking agents, calcium channel blockers, diuretics, nitrates, nicorandil and levodopa. Data were non-parametric. The median and interquartile range (IQR) of the number of drugs prescribed was calculated.

The total number of blood pressure raising agents each participant was prescribed was computed and included mirabegron and midodrine.

Frailty Index was categorised into an ordinal variable with a FI of ≤ 0.08 classified as non-frail, ≥ 0.25 was classified as frail. All other scores were classified as pre-frail. Kruskal-Wallis H test was used to compare frailty groups in the delirium and control group.

Fisher's Exact test was used to compare the delirium and control groups with regard to the proportion of males and females, the proportion of participants with cognitive impairment, admission diagnosis, medical history and prescribed medications. A chi-squared test was not carried out as the assumptions of the test were violated (expected count less than 5 in one or more cell).

In order to eliminate the effect of pre-existing cognitive impairment results were analysed for all participants and a second set of analysis was performed using only participants without pre-existing cognitive impairment. The results of participants with hyperactive and hypoactive delirium were also compared.

A significance level of $p \leq 0.05$ was set for all statistical tests.

HUT Statistical Analysis

Kruskal-Wallis test was used to assess the proportion of participants within each group that had orthostatic hypotension and orthostatic hypertension. Changes in systolic blood pressure during tilting were correlated to DRS-R98 severity (Spearman's rho) and total score (Pearson's correlation coefficient). A partial correlation was used to adjust for variables that were unequally distributed between the two groups.

Binary logistic regression was performed to assess the impact that a diagnosis of orthostatic hypotension or orthostatic hypertension would have on the likelihood of a participant being in the delirium group. Frailty status and a diagnosis of pre-existing cognitive impairment were also included in the model. Odds ratios and 95% confidence intervals (CI) were calculated.

BRS Statistical Analysis

BEI was correlated to DRS-R98 severity and total score. During calculations involving the whole group DRS-R98 severity score and erect total BEI used Spearman rho as this variable was non-parametric. Other variables were normally distributed and Pearson correlation coefficient was used.

Independent samples t-test was used to compare means in normally distributed data. Mann-Whitney U test was used to compare medians in non-parametric data. Fisher's Exact test was used to compare nominal variables. Kruskal-Wallis test was used to compare nominal to ordinal variables.

Mean BEI was also calculated for confounding variables.

Blood Pressure Variability Statistical Analysis

Mann-Whitney U test was used to compare median ARV in the whole group as data was non-parametric. Independent samples t-test was used to compare mean ARV in the subgroup without pre-existing cognitive impairment, as this data was normally distributed. A two–way between group analysis of variance was carried out to explore the relationship between delirium, hypertension and ARV.

Diurnal Blood Pressure Variability Statistical Analysis

Kruskal-Wallis test was used to compare dipping status between the two groups.

Heart Rate Variability Statistical Analysis

SDNN, RMSSD, low frequency HRV and high frequency HRV data were non-parametric variables and the Mann-Whitney U test was used to compare medians between the two groups.

3.12 Amendments to the Original Protocol

Follow-up autonomic function testing was initially planned to take place six weeks following the delirium assessment. After initial recruitment it became apparent that it would not be possible to keep to this timeline due to participants having prolonged

hospital admissions, prolonged recovery times, recurrent illnesses and the availability of testing equipment. Autonomic function testing therefore took place at a time when the participant was free of an acute illness that could impact on the results.

Ethical approval was also received to look for differences in levels of sarcopenia between the delirious and control group. This aspect of follow-up testing was not initiated due to difficulty accessing the radiology equipment required.

Chapter 4: Results

4.0 Prologue to Chapter

Chapter 4 contains the results of the study. A description of the participants initially recruited to the study is first presented. This is followed by an outline of participants who did not complete follow up. The results of Head-Up Tilt testing, baroreceptor sensitivity, 24-hour blood pressure variability, diurnal blood pressure variability and 24-hour heart rate variability are then presented separately.

4.1 Initial Participants Recruited

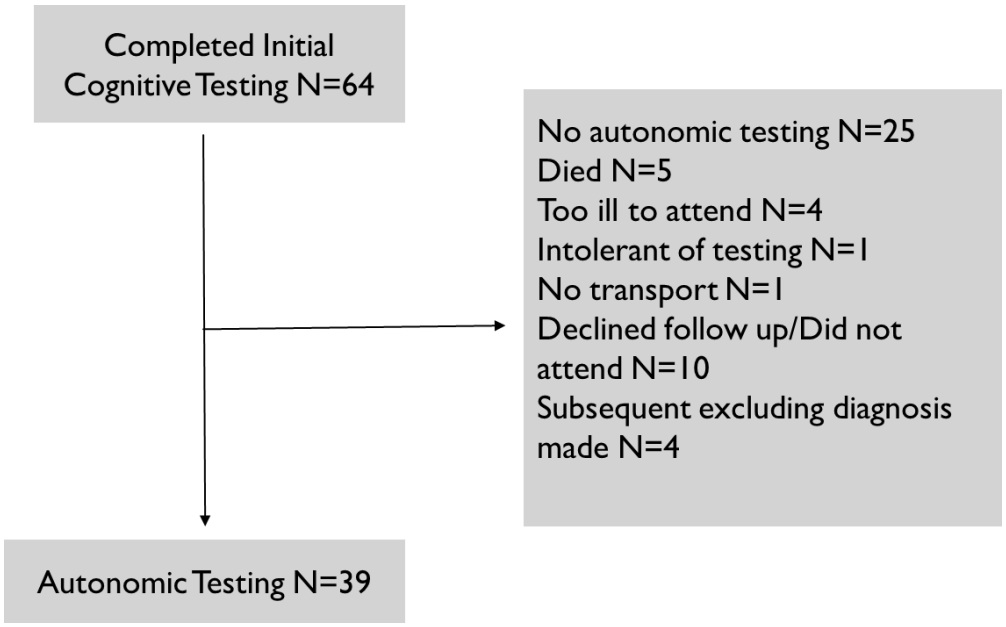
64 participants were recruited to the study and completed the initial cognitive assessments. 51.6% (33) met the diagnostic criteria for delirium.

25 participants did not attend follow-up. 30.3% (10) of the delirium group were non-attenders compared to 48.4% (15) of the control group, p=0.14. The reasons for non-attendance at follow-up are shown in Figure 8.

When those that attended follow-up were compared to those that did not attend there was no difference in age (mean 80.38 years, SD 6.41 vs mean 80.04 years, SD 7.26 respectively, p=0.84). Females accounted for 44% (11) of non-attenders and 48.7% (19) of attenders, p=0.71. A similar proportion of attenders and non-attenders had pre-existing cognitive impairment (41% vs 48%, p=0.58). 56% of non-attenders were frail. A similar proportion of those who attended follow-up were frail (51.3%, p=0.39).

Those who did not attend follow-up had a higher illness severity score, as measured by the APACHE-II with a median score of score of 8.5 (IQR 6) in those who attended and a median score of 13 in those who did not attend (IQR 6), p=0.04.

Figure 8: Reasons for Participants not Attending Follow-up



4.2 Head-Up Tilt Test Results

4.2.1 Participant Characteristics

29 patients completed Head-Up Tilt (HUT) testing. 58.6% (17) of these had a diagnosis of delirium made by DSM-IV criteria. The mean age was 80.88 years (SD 5.41) in those with delirium and 80.75 years (SD 7.39) in those without delirium (p= 0.96). Females accounted for 47.1% (8) of the delirium group and 58.3% (7) of the control group (p=0.69).

17.65% (3) of the delirious group had a pre-existing diagnosis of dementia. An additional 5.89% (1) had a positive AD8 informant questionnaire, suggestive of pre-

existing undiagnosed cognitive impairment. In the control group, no participant had a known diagnosis of dementia and 50% (6) had a positive AD8 questionnaire. Therefore, a total of 23.5% (4) participants in the delirium group and 50% (6) of the control group were classified has having pre-existing cognitive impairment (p=0.24).

Delirious participants had a higher median Frailty Index than the control group (median FI=0.3, IQR=0.12 vs median FI=0.24, IQR=0.08, p=0.01). 70.6% (12) of the delirium group and 25% (3) of the control group were classified as being frail (p=0.02). The remainder of both groups were pre-frail. There was no robust participant in either group.

Further patient characteristics are shown in Table 4 while Table 5 displays admission diagnosis. Medication use can be found in Table 6. The diagnoses precipitating admission and co-morbidities were well-matched across the delirium and control groups despite a non-randomised methodology.

Table 4: Head-Up Tilt Test-Patient Characteristics

	No Delirium	Delirium	p value
Number	12	17	
Median Charlson Comorbidity Index (IQR)	6.5 (2)	7 (2)	0.13
Median Barthel Index (IQR)	95 (IQR 14)	90 (IQR 6)	0.52
Mean APACHE II (SD)	8.57 (3.74)	10.89 (3.66)	0.23
Previous OH	25% (3)	17.7% (3)	0.69
Hypertension	50% (6)	47.1% (8)	1
Ischaemic Heart Disease	16.7% (2)	35.3% (6)	0.41
Atrial Fibrillation	33.3% (4)	41.2% (7)	0.72
Previous Stroke	0% (0)	11.8% (2)	0.49
Diabetes	16.7% (2)	23.5% (4)	1
History of Depression	8.3% (1)	0% (0)	0.41
COPD	0% (0)	35.3% (6)	0.02
CCF	25% (3)	47% (8)	0.27
Non-Smoker	75% ((9)	58.8% (10)	0.4

OH=Orthostatic Hypotension, COPD=Chronic Obstructive Pulmonary Disease, CCF=Congestive Cardiac Failure

Table 5: Head-Up Tilt Test-Admission Diagnosis

Admission Diagnosis	No Delirium	Delirium	p value
Acute Kidney Injury	8.3% (1)	17.6% (3)	0.62
Acute Liver Injury	8.3% (1)	0% (0)	0.41
Arrhythmia	0% (0)	6.7% (1)	1
Anaemia	0% (0)	11.8% (2)	0.49
Seizure	16.7% (2)	0% (0)	0.16
Infection (includes respiratory, urinary, cellulitis)	33.3% (4)	58.8% (10)	0.33
Cardiac Failure	8.3% (1)	35.3% (6)	0.19
Fall/Syncope	41.7% (5)	29.4% (5)	0.64
Hyponatraemia	8.3% (1)	6.7% (1)	1
Symptomatic Goitre	8.3% (1)	0% (0)	0.41
Pulmonary Embolus	16.7% (2)	0% (0)	0.13
Hip Fracture	0% (0)	11.8% (2)	0.5
Urinary Retention	8.3% (1)	0% (0)	0.41
Total Knee Replacement	8.3% (1)	0% (0)	0.41
Non-cardiac chest pain	0% (0)	6.7% (1)	1

Table 5 displays the number of participants in each group that had the listed admission diagnosis. Patients may have had more than one diagnosis.

Table 6: Head-Up Tilt Test-Medications on Admission

Medication	No Delirium	Delirium	p value
Alpha-blocker	0% (0)	17.6% (3)	0.23
Anticholinergic	8.3% (1)	0% (0)	0.41
Antipsychotics	25% (3)	11.8% (2)	0.62
Angiotension Converting Enzyme Inhibitor (ACE-I)	8.3% (1)	17.6% (3)	0.62
Angiotension Receptor Blocker (ARB)	25% (3)	29.4% (5)	1
Beta-Adrenergic Blocking Agent (β-Blocker)	41.7% (5)	29.4% (5)	0.64
Diuretic*	33.3% (4)	76.5% (13)	0.03
Calcium Channel Blocker	33.3% (4)	35.3% (6)	1
Donepezil	0% (0)	6.7% (1)	1
Memantine	0% (0)	11.8% (2)	0.5
Midodrine	25% (3)	11.8% (2)	0.62
Mirabegron	8.3% (1)	0% (0)	0.41
Nitrate	0% (0)	17.6% (3)	0.25
Median number of blood pressure lowering agents per person	2, range 0-3, IQR 3	2, range 1-5, IQR 1.5	0.2
Median number of blood pressure raising agents per person	0, range 0-1, IQR 1	0, range 0-1, IQR	0.13

*Includes the use of diuretics for the treatment of heart failure, liver failure or hypertension

4.2.2 HUT Results

The delirium group had a median decrease of 1mmHg (IQR 38.5) in systolic blood pressure and a median increase of 9mmHg (IQR 28) in diastolic blood pressure. The control group had a median decrease of 17.5mmHg (IQR 20.75) in systolic blood pressure and a median increase of 0.5mmHg (IQR 10) in diastolic blood pressure, p=0.04 for systolic blood pressure and p=0.15 for diastolic blood pressure.

As DRS-R98 severity scores increased systolic blood pressure change during HUT also increased (r_s= 0.42, p=0.03). A similar pattern was present for total DRS-R98 scores (r_s =0.4, p=0.03).

A partial correlation was carried out to control for variables that were unequally distributed between the two groups (cognitive impairment, Chronic Obstructive Pulmonary Disease (COPD), frailty and diuretic use). DRS-R98 severity scores maintained a similar pattern (r_s= 0.46, p=0.02). There was a non-significant correlation between DRS-R98 total score and systolic blood pressure change, r_s= 0.37, p=0.07.

35.3% (6) of patients in the delirium group had orthostatic hypotension compared to 50% (6) of the control group. 47.1% (8) of the delirium group had orthostatic hypertension compared to 8.3% (1) of the control group (p=0.14).

When a subgroup analysis of participants (19) without cognitive impairment was carried out, the rate of orthostatic hypertension was 53.8% (7) in the delirium group and no patients in the control group had orthostatic hypertension (p=0.03). This is shown in Figure 9.

4.2.3 Confounding Variables

Rates of orthostatic hypotension did not vary with gender. 53.3% (8) of females and 28.6% (4) of males had orthostatic hypotension. 20% (3) of females and 42.9% (6) of males had orthostatic hypertension while the remainder had a normal test, p=0.14.

There was no relationship between the presence of frailty, COPD or diuretic use and a diagnosis of orthostatic hypotension or orthostatic hypertension (Table 7).

Figure 9: Orthostatic Hypertension is more common in the Delirium Group

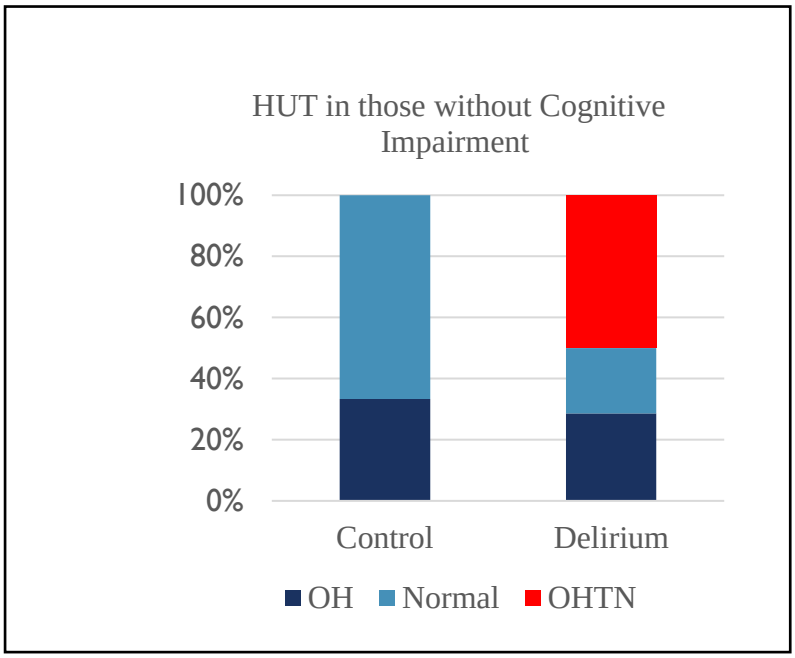


Figure 9 shows the proportion of participants without pre-existing cognitive impairment in the delirium and control group who had orthostatic hypotension and orthostatic hypertension.
HUT=Head-Up Tilt Test, OH=orthostatic hypotension, OHTN =orthostatic hypertension

Table 7: Head-Up Tilt Test-Confounding Variables

	OHTN	Normal	OH	p value
Pre-frail Frail	44.4% (4) 55.6% (5)	50% (4) 50% (4)	50% (6) 50% (6)	0.82
Diuretic use No diuretic use	44.4% (4) 55.6% (5)	62.5% (5) 37.5% (3)	66.7% (8) 33.3% (4)	0.33
COPD No COPD	22.2% (2) 77.8% (7)	25% (2) 75% (2)	33.3% (2) 16.7% (2)	0.73

Table 7 shows the proportion of participants with OHTN, OH and normal tilt test who had frailty, COPD, CCF and used diuretics.
COPD=Chronic Obstructive Pulmonary Disease, OH=Orthostatic Hypotension, OHTN=Orthostatic Hypertension, CCF=Congestive Cardiac Failure

Binary logistic regression was performed to assess the impact that orthostatic hypertension, orthostatic hypotension, frailty and pre-existing cognitive impairment had on a diagnosis of delirium. The full model was statistically significant, χ^2 (4, N=29)=15.22, p<0.01. The model explained between 40.8% (Cox and Snell R square) and 55% (Nagelkerke R squared) of the variance in delirium status and correctly classified 75.9% of cases. Both orthostatic hypertension and frailty made a unique statistically significant contribution to the model. The odds ratio of those with orthostatic hypertension having delirium was 34.06 (95% CI 1.31-893.18, p=0.03). The odds ratio of those with frailty having delirium was 15.28 (95% CI 1.6-147.75, p=0.02).

As it was felt likely that pre-existing cognitive impairment would have a significant impact on the development of delirium a model containing just cognitive impairment was carried out. This model was not significant, χ^2 (2, N=29)=2.18, p=0.14. The model was also run to assess the impact of pre-existing cognitive impairment and frailty had on a diagnosis of delirium. The overall model was significant, χ^2 (3, N=29)=8.63, p=0.01, but only frailty contributed to the model. The odds ratio of those with pre-existing cognitive impairment having delirium was 0.23 (95% CI 0.04-1.52, p=0.23)

The model was rerun using just the variables that added a significant contribution-orthostatic hypertension and frailty. The full model was statistically significant, χ^2 (3, N=29)=12.32, p<0.01. The model explained between 34.6% (Cox and Snell R square) and 46.6% (Nagelkerke R squared) of the variance in delirium status and correctly classified 79.3% of cases. Both orthostatic hypertension and frailty made a unique statistically significant contribution to the model. The odds ratio of those with orthostatic hypertension having delirium was 15.53 (95% CI 1.2-200.19, p=0.04). The odds ratio of those with frailty having delirium was 10.76 (95% CI 1.48-78.09, p=0.02).

4.2.4 Impact of Delirium Subtype on HUT results

Five participants had hyperactive delirium and six had hypoactive delirium. Participants with hyperactive delirium had a mean increase in systolic blood pressure on tilting of 9.2mmHg (SD 12.6). Hypoactive participants had a mean decrease in systolic blood pressure of 10.2mmHg (SD 20.3), p=0.1. One participant in each group had pre-existing cognitive impairment. When they were excluded the hyperactive group had a mean increase in systolic blood pressure of 13.3mmHg (SD 10) and the hypoactive group had a mean decrease of 8.6 (SD 22.3), p=0.11.

Participants with hyperactive delirium had a median increase in diastolic blood pressure on tilting of 20mmHg (IQR 20). Hypoactive participants had a median increase in DBP of 0.5mmHg (SD 23), p=0.14. When the two participants with pre-existing cognitive impairment were excluded the hyperactive group had a mean increase in diastolic blood pressure of 19.8mmHg (SD 3.4) and the hypoactive group had a mean decrease of 3.4 (SD 12.1), p=0.04.

4.3 Baroreflex Sensitivity Results

4.3.1 Participant Characteristics

25 patients completed Baroreflex Sensitivity (BRS) testing. 56% (14) of these had a diagnosis of delirium made by DSM-IV criteria. The mean age was 81.36 years (SD 5.76) in those with delirium and 79.82 years (SD 8.16) in those without delirium, t=-0.55, p= 0.59. Females accounted for 50% (7) of the delirium group and 63.6% (7) of the control group, p=0.69.

7.7% (1) of the delirious group had a pre-existing diagnosis of dementia. An additional 7.7% (1) had a positive AD8 informant questionnaire, suggesting pre-existing cognitive impairment. In the control group, no participant had a known diagnosis of dementia and 54.5% (6) had a positive AD8 questionnaire. Therefore, a total of 14.3% (2) participants in the delirium group and 54.5% (6) of the control group were classified as having pre-existing cognitive impairment (p=0.81).

Delirious participants had a median Frailty Index of 0.27 (SD 0.06). The control group had a median Frailty Index of 0.22 (SD 0.07), p= 0.06. 64.3% (9) of the delirium group and 27.3% (3) of the control group were classified as being frail (p=0.07). The remainder of both groups were pre-frail.

Further patient characteristics are shown in Table 8 while Table 9 displays admission diagnosis and medication use can be found in Table 10.

Table 8: Patient Characteristics for Baroreceptor Sensitivity Study

	No Delirium	Delirium	p value
Number	11	14	
Median Charlson Comorbidity Index (IQR)	7 (3)	7 (1)	0.32
Median Barthel Index (IQR)	92 (15)	92 (7)	0.57
Mean APACHE II (SD)	8.38 (3.5)	11 (3.89)	0.18
Hypertension	54.5% (6)	42.3% (6)	0.7
Ischaemic Heart Disease	18.2% (2)	35.7% (5)	0.41
Atrial Fibrillation	27.3% (3)	35.7% (5)	1
Previous Stroke	0% (0)	14.3% (2)	0.49
COPD	0% (0)	35.7% (5)	0.05
Diabetes	18.2% (2)	14.3% (2)	1
History of Depression	18.2% (2)	0% (0)	0.18

COPD=Chonic Obstructive Airway Disease

Table 9: Admission Diagnosis for Baroreceptor Sensitivity Study

Admission Diagnosis	No Delirium	Delirium	p value
Acute Kidney Injury	9.1% (1)	21.4% (3)	0.6
Acute Liver Injury	9.1% (1)	0% (0)	0.4
Arrhythmia	0% (0)	7.1% (1)	1
Anaemia	0% (0)	14.3% (2)	0.49
Seizure	27.3% (3)	0% (0)	0.07
Infection (includes respiratory, urinary, cellulitis)	18.2% (2)	64.3% (9)	0.04
Cardiac Failure	0% (0)	42.3% (6)	0.02
Fall/Syncope	45.5% (5)	21.4% (3)	0.39
Hyponatraemia	18.2% (2)	7.1% (1)	0.57
Symptomatic Goitre	9.1% (1)	0% (0)	0.44
Pulmonary Embolus	9.1% (1)	0% (0)	0.44
Hip Fracture	0% (0)	7.1% (1)	1
Non-cardiac chest pain	0% (0)	7.1% (1)	1

Table 9 displays the number of participants in each group that had the listed admission diagnosis. Patients may have had more than one diagnosis.

Table 10: Medications on Admission in Baroreceptor Sensitivity Study

Medication	No Delirium	Delirium	p value
Alpha-blocker	0% (0)	14.3% (2)	0.49
Anticholinergic	9.1% (1)	0% (0)	0.42
Antipsychotics	36.4% (4)	14.3% (2)	0.19
Angiotension Converting Enzyme Inhibitor (ACE-I)	9.1% (1)	14.3% (2)	1
Angiotension Receptor Blocker (ARB)	27.3% (3)	28.6% (4)	1
Beta-Adrenergic Blocking Agent (β-Blocker)	45.5% (5)	28.6% (4)	0.4
Diuretic	27.3% (3)	85.7% (12)	0.02
Calcium Channel Blocker	36.4% (4)	35.7% (5)	1
Digoxin	9.1% (1)	14.3% (2)	1
Donepezil	0% (0)	7.1% (1)	1
Memantine	0% (0)	0% (0)	
Midodrine	27.3% (3)	7.1% (1)	0.27
Mirabegron	0% (0)	0% (0)	
Nitrate	0% (0)	21.4% (3)	0.24
Median number of blood pressure lowering agents per person (IQR)	2, range 0-3, IQR=3	2 range=1-5, IQR=1.25	0.33
Median number of blood pressure raising agents per person	0 range 0-1, IQR=1	0 range 0-1, IQR=0	0.15

4.3.2 Baroreflex Sensitivity Results

BEI: All Participants

Mean BEI during the supine phase was 37.1% (SD 18.47) in the delirium group and 58.57% (SD 29.56) in the control group, p=0.06. During the tilting phase median BEI was 22.95% (IQR 44.42) in the delirium group and 46.74% (IQR 17.38) in the control group, p=0.16.

DRS-R98 severity score was negatively correlated to supine BEI, r_2=-0.44 p=0.05. The correlation between DRS-R98 total score and supine BEI was r=-0.43 p=0.05. There was no linear relationship between DRS-R98 scores and BEI during the tilting phase.

BEI: Participants with no Pre-existing Cognitive Impairment

When participants without pre-existing cognitive impairment where looked at in isolation mean supine BEI was 37.06% (SD 19.65) in the delirium group and 67.59% (SD 26.26) in the control group, p=0.03. During the tilting phase median BEI was 19.3% (IQR 47.14) in those with delirium and 50.78% (IQR 37.85) in those without delirium (p=0.14).

DRS-R98 total score was negatively correlated to supine BEI, r=-0.56 p=0.04. The correlation between DRS-R98 severity score and supine BEI was r=-0.5 p=0.07. There was no linear relationship between DRS-R98 scores and BEI during the tilting phase.

BEI-Up: All Participants

Mean supine BEI-Up was 60.63% (SD 34.28%) and 66.97% (SD 34.55%) in the delirium and control group respectively, p=0.76. Mean erect BEI-Up was 28.93% (SD 20.03) in the delirious participants compared to 43.73% (SD 22.59) in the non-delirious group, p=0.11).

DRS-R98 total score was negatively correlated to supine BEI, r=-0.56 p=0.04.

BEI-Up: Participants with no Pre-existing Cognitive Impairment

When participants without pre-existing cognitive impairment where looked at in isolation mean supine BEI-Up was 60.63% (SD 34.28) in the delirium group and 66.98% (SD 34.55) in the control group, p=0.76. During the tilting phase mean BEI

was 36.87% (SD 22.26) in those with delirium and 56.03 (SD 23.04) in those without delirium, p=0.05.

During tilting BEI-Up was non-significantly correlated to DRS-R98 total score, r=-0.49, p=0.06.

BEI-Down: All Participants

Mean supine BEI-Down was 40.01% (SD 16.65) and 65.91% (SD 22.8) in the delirium and control groups respectively, p=0.04. During tilting Mean BEI-Down was 41% (SD 26.81) and 50.8% (SD 23.47) in the delirium and control groups respectively, p= 0.36.

BEI-Down: Participants with no Pre-existing Cognitive Impairment

When participants without pre-existing cognitive impairment where looked at in isolation mean supine BEI-Down was 40.97% (SD 17.74) in the delirium group and 65.91% (SD 22.8) in the control group, p=0.04. During the tilting phase mean BEI was 38.71% (SD 25.97) in those with delirium and 61.25% (SD 26.05) in those without delirium, p=0.21.

Supine BEI-Down was non-significantly correlated to DRS-R98 total score, r=-0.5, p=0.08.

A summary of the BEI scores in participants without pre-existing cognitive impairment is shown in Figure 10.

Figure 10: Baroreflex Effectiveness Index in Participants with Normal Baseline Cognition

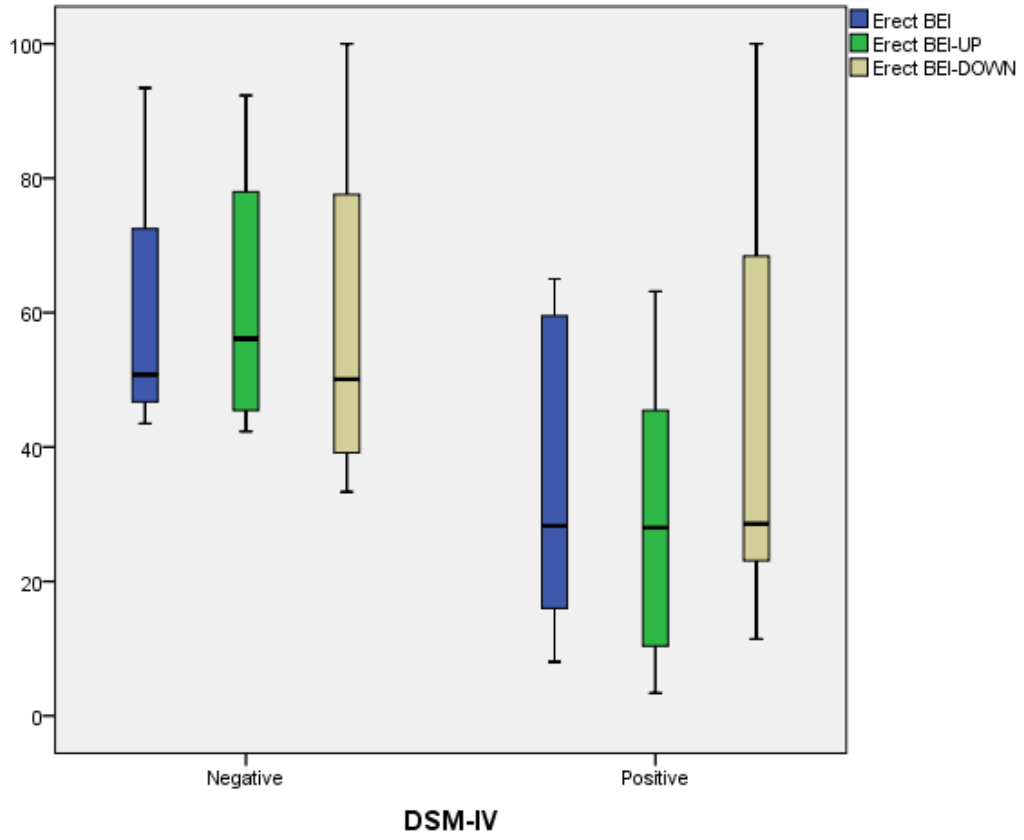


Figure 10 compares Baroreflex Effectiveness Index in the delirium and control groups during the tilting phase of the Head-Up Tilt test. BEU-Up is the proportion of increases in blood pressure followed by an appropriate decreased in heart rate. BEI-Down is the proportion of decreases in blood pressure followed by an appropriate increase in heart rate.

4.3.3 Impact of Delirium Subtype

A comparison of BEI in participants with hyperactive and hypoactive delirium is shown in Table 11. Participants with mixed delirium are not included in the analysis.

Table 11: Comparison of Baroreflex Effectiveness Index in Hyperactive and Hypoactive Delirium

	Hyperactive N=5	Hypoactive N=5	p value
Mean Supine BEI (SD)	35.31% (16.62)	29.56% (19.36)	0.67
Median Erect BEI (IQR)	28.26% (43.27)	25.5% (30.62)	0.25
Mean Supine BEI-Up (SD)	64.3% (35.47)	27.09 (20.63)	0.25
Mean Erect BEI-Up (SD)	35.39% (17.48)	21.46 (26.73)	0.38
Mean Supine BEI-Down (SD)	36.06% (12.91)	38.15 (22.33)	0.95
Mean Erect BEI-Down (SD)	53.31% (33.84)	34.33% (21.34)	0.37

4.3.4 Confounding Factors and BEI

Mean BEI was calculated for the variables that were found to be unequally distributed in Tables 9,10 and 11. The results are shown in Table 12.

Table 12: Confounding Variables for Baroreceptor Sensitivity Study

	Supine BEI	Erect BEI	Supine BEI-Up	Erect BEI-Up	Supine BEI-Down	Erect BEI-Down
Frail Pre-frail	40.29% (15.47) 53.44% (27.05) p=0.72	40.22% (26.14) 47.4% (19.98) p=0.68	54.45% (30.93) 53.92% (30.94) p=0.97	33.19% (17.45) 38.6% (26.21) p=0.57	48.44% (17.97) 49.14% (26.79) p=0.95	47.25% (28.18) 44.01% (23.63) p=0.76
Diuretic Use No diuretic use	44.74 (24.16) 50.8% (30.94) p=0.65	39.5% (24.27) 47.4% (19.98) p=0.99	53.71% (35.84) 54.88% (32.74) p=0.95	34.77% (24.04) 37.37% (20.92) p=0.79	47.49% (24.1) 50.34% (22.84) p=0.8	46.75% (28.65) 43.74% (21.02) p=0.78
COPD No COPD	32.5% (27.3) 52% (26.7) p=0.21	23.3% (19.7) 42.6% (22.4) p=0.1	57.76% (57.74) 53.72% (32.33) p=0.89	20.73% (17.99) 39.23% (21.95) p=0.13	31.79% (18.35) 53.4% (22.29) p=0.09	31.01% (23.56) 49.31% (24.9) p=0.15
CCF No CCF	43.3% (20.2) 52.2% (26.6) p=0.57	39.2% (25.2) 47.8% (20.2) p=0.41	46.43% (37.3) 51.4% (34.7) p=0.62	34.5% (23) 46.7% (24.5) p=0.52	Median (IQR) 48.3% (55.1) 46.2% (19.1) p=0.3	44.9% (29.8) 49.3% (20.5) p=0.35
Infection	47.8% (22.2) 50.2% (26.1) p=0.35	48.6% (20.6) 44.4% (22.1) p=0.32	52.4% (43.2) 49.3% (33.6) p=0.42	42.5% (20.2) 43.4% (25.7) p=0.17	46.7% (15.3) 51.6% (23.9) p=0.59	56% (24.2) 45.8% (22.5) p=0.67

Table 12 shows a comparison of BEI between those with pre-frailty and frailty, diuretic and non-diuretic use and participants with and without COPD (Chronic Obstructive Pulmonary Disease), CCF (Congestive Cardiac Failure) and a diagnosis of infection on admission. All values are mean (SD) unless stated otherwise.

4.4 Blood Pressure Variability

4.4.1 Patient Characteristics

35 patients completed blood pressure variability (BPV) testing. 60% (21) of these had a diagnosis of delirium made by DSM-IV criteria. The mean age was 81.3 years (SD 6.1) in those with delirium and 80 years (SD 7.3) in those without delirium (p=0.49). Females accounted for 42.9% (9) of the delirium group and 71.4% (10) of the control group (p=0.1).

9.5% (2) of the delirious group had a pre-existing diagnosis of dementia. An additional 23.81% (5) had a positive AD8 informant questionnaire. In the control group, 1 participant (7.1%) had a known diagnosis of dementia and 42.86% (6) had a positive AD8 questionnaire. Therefore, a total of 33.3% (7) participants in the delirium group and 50% (7) of the control group were classified as having pre-existing cognitive impairment (p=0.32).

Delirious participants had a median Frailty Index of 0.29 (IQR 0.08). The control group had a median Frailty Index of 0.21 (IQR 0.07), p= 0.03. 71.4% (15) of the delirium group and 21.4% (3) of the control group were classified as being frail (p<0.01). The remainder of both groups were pre-frail.

24-hour mean systolic blood pressure was 129.95mmHg (SD 17.68) in the delirium group and 139.36mmHg (SD 22.39) in the control group (p=0.18). Mean 24-hour diastolic blood pressure was 72.5mmHg (SD 11.43) in the delirium group and 74mmHg (SD 10.13) in the control group (p=0.7).

Further patient characteristics are shown in Table 13 while Table 14 displays admission diagnosis and medication use can be found in Table 15.

Table 13: Blood Pressure Variability-Patient Characteristics

	No Delirium	Delirium	p value
Number	14	21	
Median Charlson Comorbidity Index (IQR)	6 (3)	6.5 (2)	0.25
Mean Barthel Index (SD)	91.31 (8.14)	92.38 (5.57)	0.68
Mean APACHE II (SD)	8.38 (3.5)	10.89 (3.66)	0.17
Hypertension	61.5% (8)	57.1% (12)	1
Ischaemic Heart Disease	14.3% (2)	38.1% (8)	0.25
Atrial Fibrillation	21.4% (3)	33.3% (7)	0.7
CCF	7.1% (1)	23.8% (5)	0.37
Previous Stroke	0% (0)	14.3% (3)	0.27
Parkinson's Disease	7.1% (1)	0% (0)	0.4
COPD	0% (0)	28.6% (6)	0.06
CKD	0% (0)	4.8% (1)	1
Diabetes	11.8% (2)	14.3% (3)	1
History of Depression	11.8% (2)	0% (0)	0.13

Table 14: Blood Pressure Variability-Admission Diagnosis

Admission Diagnosis	No Delirium	Delirium	p value
Acute Kidney Injury	7.1% (1)	14.3% (3)	0.64
Acute Liver Injury	7.1% (1)	0% (0)	0.4
Arrhythmia	0% (0)	9.5% (2)	0.51
Anaemia	0% (0)	9.5% (2)	0.51
Seizure	21.4% (3)	0% (0)	0.06
Infection (includes respiratory, urinary, cellulitis)	28.6% (4)	66.7% (14)	0.09
Cardiac Failure	0% (0)	33.3% (7)	0.03
Fall/Syncope	35.7% (5)	33.3% (7)	1
Hyponatraemia	11.8% (2)	9.5% (2)	1
Symptomatic Goitre	7.1% (1)	0% (0)	0.4
Pulmonary Embolus	7.1% (1)	0% (0)	0.4
Hip Fracture	0% (0)	9.5% (2)	0.51
Non-cardiac chest pain	0% (0)	4.8% (1)	1
Urinary Retention	7.1% (1)	0% (0)	0.4

Table 14 displays the number of participants in each group that had the listed admission diagnosis. Patients may have had more than one diagnosis.

Table 15: Blood Pressure Variability-Medications on Admission

Medication	No Delirium	Delirium	p value
Alpha-blocker	0% (0)	9.5% (2)	0.51
Anticholinergic	7.1% (1)	0% (0)	0.38
Antipsychotics	28.6% (4)	14.3% (3)	0.38
Angiotension Converting Enzyme Inhibitor (ACE-I)	11.8% (2)	9.5% (2)	0.63
Angiotension Receptor Blocker (ARB)	28.6% (4)	28.6% (6)	1
Beta-Adrenergic Blocking Agent (β-Blocker)	35.7% (5)	23.8% (5)	0.45
Diuretic	21.4% (3)	80.1% (17)	0.01
Calcium Channel Blocker	28.6% (4)	28.6% (6)	1
Donepezil	7.1% (1)	4.8% (1)	1
Memantine	0% (0)	4.8% (1)	1
Midodrine	7.1% (1)	0% (0)	0.65
Mirabegron	7.1% (1)	0% (0)	0.38
Nicorandil	0% (0)	4.8% (1)	1
Nitrate	0% (0)	14.3% (3)	0.27
Median number of blood pressure lowering agents per person	2, range 0-3, IQR 2.5	2, range 0-5, IQR 1.5	0.3
Median number of blood pressure raising agents per person	0, range 1-1, IQR 1	0, range 0-1, IQR 0	0.26

4.4.2 BPV Results

All Participants

Median ARV was 12.71 (IQR 5.58) in the control group and 9.93 (IQR 4.85) in the delirium group (p=0.12).

Within the delirious group the mean ARV in those with hyperactive delirium was 12.74 (SD 2.79) and it was 9.06 (SD 3.39) in those with hypoactive delirium (p=0.05).

Participants Without Cognitive Impairment

In those without pre-existing cognitive impairment mean ARV was 13.81 (SD 5.98) in the control group and 9.69 (SD 2.75) in the delirium group (p=0.05).

4.4.3 Confounding Variables and BPV

When other diagnosis and medication use that could impact on BPV were analysed only hypertension was found to impact on ARV (Table 16). Participants within the hypertensive group who had delirium had a mean ARV of 10.8 (SD 2.2). Those with hypertension and no delirium had a mean ARV of 16.3 (SD 6.9), p=0.06.

A two–way between group analysis of variance was carried out to explore the relationship of delirium and hypertension on ARV in participants without pre-existing cognitive impairment. The interaction effect between hypertension and delirium was not significant, F=0.53, p=0.48. There was a statistically significant main effect for delirium, F=5.29, p=0.04, partial eta squared=0.25. The main effect for hypertension was also significant, F= 5.06, p=0.04, partial eta squared=0.24.

Table 16: Relationship Between Average Real Variability and Confounding Variables

	No	Yes	
Hypertension	No=15 ARV=8.83 IQR=5.21	No=21 ARV=12.51 IQR=4.98	0.05
Ischaemic heart disease	No=24 ARV=11.85 SD=4.77	No=11 ARV=11.67 SD=2.85	0.91
Congestive cardiac failure	No=24 ARV=12.2 IQR=4.6	No=12 ARV=9.4 IQR=4.9	0.09
Orthostatic hypotension	No=29 ARV=11.92 SD=4.42	No=7 ARV=10.55 SD=2.54	0.47
Previous cerebrovascular accident	No=33 ARV=12.01 SD=4.41	No=3 ARV=9.86 SD=0.97	0.41
Diabetes	No=31 ARV=11.29 IQR=5.33	No=5 ARV=12.38 IQR=11.22	0.93
Alpha-blocker	No=34 ARV=11.92 IQR=5.33	No=2 ARV=10.19 IQR=	0.59
Angiotension Converting Enzyme Inhibitor (ACE-I)	No=35 ARV=11.6 IQR=5.32	No=4 ARV=9.7 IQR=	0.33
Angiotension Receptor Blocker (ARB)	No=26 ARV=10.97 IQR=5.56	No=10 ARV=11.6 IQR=4.42	0.83
Beta-Blocker	No=26 ARV=9.92 IQR=3.7	No=10 ARV=12.71 IQR=5.19	0.15
Calcium Channel Blocker	No=26 ARV=9.74 IQR=6.14	No=10 ARV=12.38 IQR=2.69	0.16
Diuretics	No=18 ARV=12.52 IQR=5.29	No=18 ARV=10.37 IQR=4.44	0.93
Midodrine	No=29 ARV=12.23 IQR=5.35	No=6 ARV=9.21 IQR=2.61	0.13
Nitrate	No=33 ARV=11.6 IQR=5.21	No=3 ARV=9.82 IQR=	0.13

4.5 Diurnal Blood Pressure Variability

4.5.1 Participant Characteristics

The participants for this part of the study are the same as those who completed BPV testing and thus their characteristics can be found in Section 5.4.

4.5.2 Diurnal Blood Pressure Variability Results

All Participants

Within the delirium group, 57.9% (11) of participants were reverse dippers, 26.3% (5) were non-dippers, 10.5% (2) had a normal dipping pattern and 5.3% (1) was an extreme dipper.

In the control group 35.7% (5) were reverse dippers, 35.7% (5) were non-dippers, 14.3% (2) had a normal dipping pattern and 14.3% (2) were extreme dippers. There was a non-significant difference between the two groups, p=0.19.

Participants Without Pre-existing Cognitive Impairment

Within the delirium group, 58.3% (7) of participants were reverse dippers, 33.3% (4) were non-dippers and 8.3% (1) had a normal dipping pattern. No participant was an extreme dipper.

In the control group no participant was a reverse dipper, 57.1% (4) were non-dippers, 14.3% (1) had a normal dipping pattern and 28.6% (2) were extreme dippers. There was a significant difference between the two groups, p=0.01 (Figure 11).

Figure 11: Blood Pressure Dipping Status in Participants without Pre-existing Cognitive Impairment

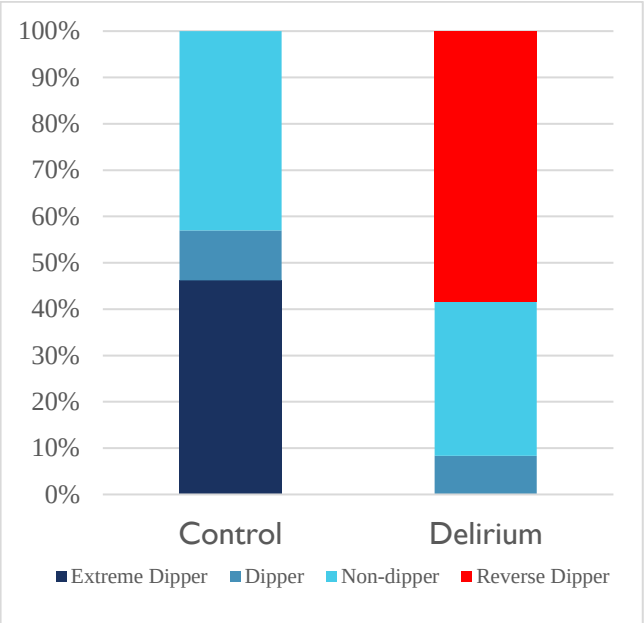


Figure 11 shows the dipping in the delirium group compared to the control group in the subgroup without cognitive impairment (N=21). Within the delirium group no participant was an extreme dipper. All participants who were extreme dippers were in the control group.

4.5.3 Confounding Variables

There was no relationship between dipping status and any of the following variables: frailty or pre-frailty (p=0.27), pre-existing cognitive impairment (p=0.58), COPD (p=0.5), ischaemic heart disease (p=0.29), hypertension (p=0.41) or diuretic use (p=0.85).

4.5.4 Effect of Delirium Subtype on Dipping Status

Six participants had hyperactive delirium. 66.7% (4) were reverse dippers. None of these had pre-existing cognitive impairment. Of the remaining two participants with hyperactive delirium one was a dipper and one was an-extreme dipper. Both of these participants had pre-existing cognitive impairment.

Four participants had hypoactive delirium. None of these had pre-existing cognitive impairment. 50% (2) were reverse dippers, 1 was a non-dipper and 1 was a normal dipper.

No statistically significant relationship between hypoactive and hyperactive delirium was identified, p=0.9 for all participants and p=0.13 for those without pre-existing cognitive impairment.

4.6 Heart Rate Variability

4.6.1 Patient Characteristics

26 patients completed Heart Rate Variability (HRV) testing. 65.2% (17) of these had a diagnosis of delirium made by DSM-IV criteria. The mean age was 80.2 years (SD 5.1) in those with delirium and 80.1 years (SD 7.5) in those without delirium (p= 0.85). Females accounted for 41.2%% (7) of the delirium group and 77.8% (7) of the control group (p=0.1).

5.9% (1) of the delirious group had a pre-existing diagnosis of dementia. An additional 17.6% (3) had a positive AD8 informant questionnaire. In the control group, 1 participant (11.1%) had a known diagnosis of dementia and 44.4% (4) had a positive AD8 questionnaire. Therefore, a total of 23.5% (4) participants in the delirium group and 55.6% (5) of the control group were classified has having pre-existing cognitive impairment (p=0.19).

Delirious participants had a median Frailty Index of 0.33 (IQR 0.12). The control group had a median Frailty Index of 0.24 (IQR 0.12), p=0.01. 70.6% (12) of the delirium group and 11.1% (1) of the control group were classified as being frail (p=0.01). The remainder of both groups were pre-frail.

Within the delirium group four participants had hyperactive delirium and seven participants had hypoactive delirium.

Further patient characteristics are shown in Table 17 while Table 18 displays admission diagnosis and medication use can be found in Table 19.

Table 17: Heart Rate Variability-Patient Characteristics

	No Delirium	Delirium	p value
Number	9	17	
Mean Charlson Comorbidity Index (SD)	6 (1.15)	6.7 (1.49)	0.29
Mean Barthel Index (SD)	92.13 (9.48)	92.46 (5.25)	0.92
Mean APACHE II (SD)	9 (3.68)	11.38 (3.58)	0.25
Hypertension	55.6% (5)	55.9% (9)	1
Ischaemic Heart Disease	22.2% (2)	33.5% (6)	0.67
CCF	0% (0)	23.5% (4)	0.27
Previous Stroke	0% (0)	11.8% (2)	1
COPD	0% (0)	41.2% (7)	0.06
CKD	0% (0)	5.9% (1)	1
Diabetes	11.1% (1)	17.6% (3)	1
History of Depression	11.1% (1)	5.9% (1)	1

Table 18: Heart Rate Variability-Admission Diagnosis

Admission Diagnosis	No Delirium	Delirium	p value
Acute Kidney Injury	0% (0)	17.6% (3)	0.53
Acute Liver Injury	11.1% (1)	0% (0)	0.35
Arrhythmia	0% (0)	11.8% (2)	0.53
Anaemia	0% (0)	11.8% (2)	0.53
Seizure	22.2% (2)	0% (0)	0.11
Infection (includes respiratory, urinary, cellulitis)	22.2% (2)	70.6% (12)	0.04
Cardiac Failure	0% (0)	33.5% (6)	0.06
Fall/Syncope	33.3% (3)	33.5% (6)	1
Hyponatraemia	22.2% (2)	11.8% (2)	0.59
Symptomatic Goitre	11.1% (1)	0% (0)	0.5
Pulmonary Embolus	11.1% (1)	0% (0)	0.5
Hip Fracture	0% (0)	5.9% (1)	1

Table 18 displays the number of participants in each group that had the listed admission diagnosis. Patients may have had more than one diagnosis.

Table 19: Heart Rate Variability-Medications on Admission

Medication	No Delirium	Delirium	p value
Alpha-blocker	0% (0)	17.6% (3)	0.53
Anticholinergic	7.1% (1)	0% (0)	0.32
Antipsychotics	33.3% (3)	23.5% (4)	0.66
Angiotension Converting Enzyme Inhibitor (ACE-I)	11.1% (1)	5.9% (1)	1
Angiotension Receptor Blocker (ARB)	33.3% (3)	29.4% (5)	1
Beta-Adrenergic Blocking Agent (β-Blocker)	22.2% (2)	23.5% (4)	1
Diuretic	22.2% (2)	70.6% (12)	0.04
Calcium Channel Blocker	33.3% (3)	29.4% (5)	1
Digoxin	0% (0)	5.9% (1)	1
Donepezil	7.1% (1)	0% (0)	0.35
Memantine	0% (0)	5.9% (1)	1
Midodrine	7.1% (1)	5.9% (1)	1
Nicorandil	0% (0)	5.9% (1)	1
Nitrate	0% (0)	17.6% (3)	0.53

4.6.2 HRV Results

SDNN

Median SDNN was 105.59 (IQR 412.02) in the delirium group and 86.6 (IQR 925.91) in the control group, p=0.67. When participants with pre-existing cognitive impairment were excluded median SDNN was 216.38 (IQR 479.92) in the delirium group and 956.12 (IQR 1136.52) in the control group, p=0.14. There was no difference between participants with hyperactive (median 90.45, IQR 1216.5) and hypoactive (median 216.38, IQR 400.43) delirium, p=0.85.

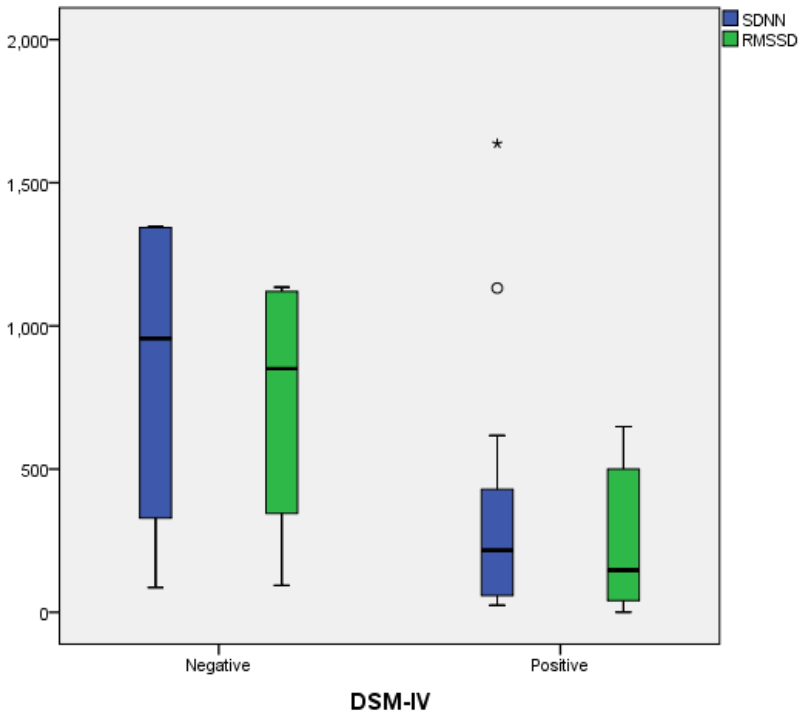
RMSSD

Median RMSSD was 114.9 (IQR 492.42) in the delirium group and 94.1 (IQR 809.82) in the control group, p=0.4. When participants with pre-existing cognitive impairment

were excluded median RMSSD was 147.22 (IQR 486.27) in the delirium group and 851.27 (IQR 908.15) in the control group, p=0.5. There was no difference between participants with hyperactive (mean 234.78, SD 280.39) and hypoactive (mean 273.49, SD 226.84) delirium, p=0.81.

SDNN and RMSSD results displayed shown in Figure 12.

Figure 12: Heart Rate Variability in Participants with Normal Baseline Cognition



SDNN represents overall heart rate variability while RMSSD represents parasympathetic components. Both are lower in the delirium group.

Low Frequency HRV (LFHRV)

Median LFHRV was 1,560.5 Hz (IQR 122,667) in the delirium group and 18,746 Hz (IQR 978,291) in the control group, p=0.61. When participants with pre-existing cognitive impairment were excluded median LFHRV was 23,352 Hz (IQR 122,270.5) in the delirium group and 978,560 Hz (IQR 1,869,835.5) in the control group, p=0.06. There was no difference between participants with hyperactive (median 1,287.75 Hz, IQR 894,734.88) and hypoactive (median 23,352Hz, IQR 100,906) delirium, p=0.85.

High Frequency HRV (HFHRV)

Median HFHRV was 5,804.5 (IQR 399,903.5) in the delirium group and 2,906Hz (IQR 3,067,654.5) in the control group, p=0.65. When participants with pre-existing cognitive impairment were excluded median HFHRV was 21,820Hz (IQR 1,100,157.5) in the delirium group and 3,068,000Hz (IQR 5,066,970.5) in the control group, p=0.09. There was no difference between participants with hyperactive (median 4,309.25Hz, IQR 3,003,231.61) and hypoactive (median 21,820Hz, IQR 1,732,540) delirium, p=0.85.

LF/HF

The median LF/HF ratio was 0.47 (IQR 0.53) in the delirium group and 0.74 (IQR 2.46) in the control group (p=0.5). When participants with pre-existing cognitive impairment were excluded the median LF/HF ratio was 0.37 (IQR 0.46) in the delirium group and 0.35 (IQR 4.62) in the control group (p=0.82). There was no difference between participants with hyperactive (median 0.33, IQR 0.62) and hypoactive (median 0.63, IQR 0.31) delirium, p=0.58.

4.6.3 Confounding Variables

Table 20 shows HRV in variables that are unequally distributed between the two groups.

Table 20: Heart Rate Variability and Confounding Variables

	SDNN	RMSSD	LFHRV	HFHRV
Pre-frail	58 (486.11)	50.03 (467.65)	1054.5 (138,951)	1,595 (836,165)
Frail	216.38 (505.11) p=0.7	279.41 (535.11) p=0.4	23,352 (381,396) p=0.59	21,820 (1,031,775) p=0.86
Infection	50.01 (306.37)	47.77 (274.94)	1,033 (60,270) 124,790	1,058 (154,994)
No infection	438.97 (1,110) p=0.2	504.2 (584.02) p=0.08	(974,616) p=0.17	486,935 (3,688,068) p=0.15
Diuretic use	261 (466)	213.3 (484.6)	31,835 (131,945)	86,140 (915,029)
No diuretic use	58.7 (514) p=0.57	72.07 (547.6) p=0.96	767.5 (277,646) p=0.5	1,667 (855,224) p=0.47

Chapter 5:
Discussion

5.0 Prologue to Chapter

Chapter 5 begins by summarising the findings of this study. I then discuss possible mechanisms to explain the results, directions for future study and the strengths and weaknesses of the study.

5.1 Summary and Interpretation of Results

5.1.1 Head-Up Tilt Test

The results of this study show that participants with recent delirium have higher rates of orthostatic hypertension and less orthostatic hypotension than participants without delirium. This was most pronounced when participants with pre-existing cognitive impairment were excluded and the delirium group were compared to controls with baseline and current normal cognition.

Participants with orthostatic hypertension had an odds ratio of 34 of being in the delirium group, even when frailty and pre-existing cognitive impairment were included in the model. The odds ratio was associated with a wide confidence interval. This reflects the small sample size. Due to the sample size more factors were not included in the analysis.

Blood pressure changes during HUT were correlated with delirium severity based on DRS-R98 scores, with participants with more severe delirium having greater increases in blood pressure. This indicates a possible exposure-response relationship.

Diuretic use was higher in the delirium groups compared to the control group. There was no statistically significant difference in other antihypertensive use. There was however a trend towards higher use of alpha-blockers and nitrates in the delirium group. As these medications can cause orthostatic hypotension (Chapple 2005;

Milazzo *et al.* 2012), they would not have contributed to the higher rate of orthostatic hypertension in the delirium group.

Part of the hypothesis of this study was that the delirium group would have higher rates of orthostatic hypotension and may be predisposed to cognitive changes due to decreases in cerebral perfusion on standing. The results of the study indicate that the reverse is true, delirium is associated with increases in blood pressure on standing. This does however still support the main hypothesis-that delirium is associated with abnormal autonomic function. Previous studies have shown that orthostatic hypertension is associated with autonomic impairment, reduced baroreceptor sensitivity and excess sympathetic activity (Chhabra and Spodick 2013). Excessive sympathetic activity is associated with cerebral vasoconstriction (Tameem and Krovvidi 2013) which supports the hypothesis that delirium may be assoicated with reduced cerebral perfusion.

In summary, the results of the HUT part of this study suggest that participants with delirium may have abnormal autonomic function and in particular may have excess sympathetic activity.

5.1.2 Baroreflex Sensitivity

This study identified reduced baroreceptor function, as measured by Baroreflex Effectiveness Index (BEI), in participants with delirium compared to controls. This is particularly true when the impact of pre-existing cognitive impairment is excluded. BEI also correlates with delirium severity with participants with more severe delirium having reduced BEI.

Supine BEI was lower in participants with delirium and no pre-existing cognitive impairment. This was driven by the impact of BEI-Down which is the proportion of

reductions in blood pressure that are followed by an appropriate increase in heart rate. There was no difference identified in BEI-Up. The conclusion in my study population is that reductions in blood pressure are not followed by a corrective increase in heart rate in the delirium group compared to the control group. This implies either an impairment of sympathetic nervous system activation or excess parasympathetic activity.

During the tilting phase of the test there was a non-significant difference in BEI between the groups but a difference was detected in BEI-Up, with delirious participants having lower values. There was no difference in BEI-Down. Therefore, during tilting increases in blood pressure were not followed by an appropriate corrective reduction in heart rate. This implies either excess sympathetic activity or a failure of parasympathetic activation.

The results of the supine BEI and the BEI measured during tilting are not congruent. The small sample size may have impacted on the results.

5.1.3 Nocturnal Blood Pressure Dipping Status

This study also identified that participants with delirium are more likely to have a reverse nocturnal dipping pattern of blood pressure compared to controls with no pre-existing cognitive impairment. Both the delirium and control groups had similar rates of diagnosed hypertension, similar use of antihypertensives and similar 24-hour mean blood pressure. The results suggest that delirium may be associated with abnormally high nocturnal sympathetic nervous system activity.

5.1.4 24-Hour Blood Pressure Variability

This study found that among participants with no pre-existing cognitive impairment, 24-hour blood pressure variability, as measured by average real variability (ARV),

was lower in the delirium compared to the control group. This difference was largely driven by a lower ARV in hypoactive delirious participants, suggesting that participants with hypoactive, but not hyperactive delirium, may have lower sympathetic nervous system activity. Patients with hypoactive and hyperactive delirium may have different autonomic nervous system profiles and should be investigated separately in future studies.

5.1.5 24-Hour Heart Rate Variability

This study identified no difference in 24-hour Heart Rate Variability when comparing the delirium and control groups, regardless of pre-existing cognitive status. There was however a trend towards delirious participants having lower HRV and in particular hypoactive participants tended to have higher HFHRV (reflecting higher parasympathetic activity) and hyperactive participants had higher LFHRV (reflecting higher sympathetic activity).

The lack of a statistically significant finding is similar to the results found in a previous study of short term heart rate variability in an ICU setting (Zaal *et al.* 2014). The inability to detect a difference between the two groups may relate to the small sample size used in both studies.

A post hoc test was carried out to determine the effect size for LFHRV (r=0.1) and HFHRV (r=0.09), indicating a small effect size. When the effect size for participations without pre-existing cognitive impairment was calculated there was found to be a moderate effect size (r=0.38 for HFHRV and r=0.38 for LFHRV).

Following the commencement of this work, Oh et al published the findings of their study which showed that HRV analysis of daily ECGs of 140 patients in an ICU could

be used to predict the development of delirium (Oh *et al.* 2018). The difference in findings between these studies may relate to the larger sample size used by Oh et al.

5.1.6 Impact of Delirium Subtype

During tilt testing the hyperactive participants had an overall increase in both systolic and diastolic blood pressure while hypoactive participants had an overall reduction in blood pressure. The difference was only statistically significant for diastolic changes in participants with no pre-existing cognitive impairment. This may reflect higher sympathetic activity in the hyperactive group.

Supine BEI-Up was non-statistically higher in hyperactive compared to hypoactive participants. This may imply that hyperactivity is associated with higher sympathetic or lower parasympathetic activity than hypoactivity.

Excluding those participants with pre-existing cognitive impairment, all of the hyperactive participants displayed a reverse nocturnal blood pressure dipping pattern. This compares to half of hypoactive participants displaying the same pattern. Again, this may suggest higher sympathetic activity in hyperactive participants.

24-hour blood pressure variability was lower in hypoactive compared to hyperactive participants. This suggests lower sympathetic activity in the hypoactive group.

Although there was no statistically significant difference detected between the hyperactive and hypoactive groups when looking at HRV there was a trend towards higher parasympathetic components (HFHRV) in the hypoactive group.

The validity of these comparisons is greatly limited by the very small sample size of the subgroups. Observation of the data does however provide an interesting hypothesis

that hyperactive and hypoactive delirium may differ in autonomic abnormalities with the difference in clinical presentation reflecting alterations in sympathetic and parasympathetic balance.

5.1.7 Combining the Results

Overall the results suggest that delirious participants have altered autonomic nervous system function when compared to participants with normal cognition. Whether these alterations reflect abnormalities in sympathetic or parasympathetic function are not consistent across the tests. The general trend of my research would suggest a pattern of sympathetic over-activity in hyperactive delirium patients. The severity of the autonomic changes also correlated with the severity of delirium. The hypoactive and hyperactive delirium groups have different patterns noted on autonomic testing. Larger studies would improve the statistical reliability of the results.

5.2 Clinical Implication of Results

The results of this study show an association between delirium and autonomic impairment. This relationship may be causal in the development of delirium or may be a manifestation of the brain dysfunction that predisposes to, or results from delirium. Further longitudinal studies would be required to further evaluate this relationship.

Reverse blood pressure dipping and orthostatic hypertension can reflect sympathetic overactivity. Patients with delirium can display clinical features that include insomnia and agitation. These are also recognised as features of excess sympathetic activity (Castro-Diehl *et al.* 2016; Lump and Moyer 2014). This raises the possibility that at least some of the clinical manifestations of delirium may relate to abnormalities in the autonomic nervous system. This could therefore, provide a target for the treatment of

these signs and symptoms as current pharmacological treatments for delirium, such as anti-psychotics, treat behavioural symptoms rather than targeting the cause of the symptoms.

If delirium is related to sympathetic overactive it would be expected that treatment with beta-adrenergic blocking agents would have a positive impact on the development of delirium and/or the severity or delirium. One study (O'Neal et al. 2017) compared the incidence of postoperative delirium in patients who did or did not receive beta-blockers in the 24-hour period prior to cardiac surgery. They reported no difference in delirium incidence between the two groups. A second study (Tse et al. 2015) retrospectively identified the risk factors for development of delirium post cardiac surgery. Preoperative beta-blocker use was associated with an odds ratio for delirium development of 1.7. The use of postoperative beta-blockers was not analysed in either of the two studies. If beta-adrenergic blockade was to impact on the development of delirium it is likely that persistent treatment during an acute illness would be required. It is also important to note that not all beta-blockers have equal ability to cross the blood-brain barrier. Highly lipophilic agents such as propranolol would have greater CNS activity (McAinsh and Cruickshank 1990) and therefore be more likely to have a positive impact on the development of delirium.

The association between delirium and autonomic impairment provides an interesting hypothesis for the benefits of centrally acting selective alpha-2 receptor agonist medications for the treatment of delirium. These alpha-2 agonists, such as clonidine and dexmedetomidine, inhibit central sympathetic outflow (Giovannitti *et al.* 2015). Dexmedetomidine is an intravenous preparation so its use is largely confined to the ICU setting. Its use results in more delirium free days than sedation with lorazepam (Pandharipande *et al.* 2007). The Oslo Study of Clonidine in Elderly Patients with Delirium is a randomised controlled trial that is investigating the use of clonidine in older adults with delirium. Initial results of haemodynamic response suggest its use is

safe in this population (Hov *et al.* 2018). If the outcome is positive, it will further support role of the autonomic nervous system in delirium. Moxonidine is a I1-imidazoline receptor agonist that acts in the medulla to reduce sympathetic activity. It is used in the treatment of hypertension (Ziegler et al. 1996). Surveillance evidence suggests it may cause sedation in some patients (Schachter 1999). It's impact on delirium is not reported.

Delirium prevention is an important aspect of the clinical care of older adults. By identifying at risk individuals, preventative measures can be focused on those who require it. If further research confirms the association between delirium and autonomic impairment, it may possible to identify individuals at high risk of delirium at their initial presentation. Following the initiation of this thesis, Oh et al published the findings of their research showing the changes in heart rate variability could be used to predict the development of delirium (Oh *et al.* 2018).

5.3 Possible Vascular Implication of the Results

Reverse blood pressure dipping is an alteration in the normal circadian blood pressure pattern. It is present in approximately 3% of the general population and is more commonly seen in those with hypertension. It is associated with markers of end organ damage including the development of proteinuria, coronary calcification and left ventricular hypertrophy. It is a predictor of the presence of mild carotid plaques and is associated with arterial stiffness (Cuspidi *et al.* 2017). Reverse dipping in delirious participants in this study may therefore be a marker of occult cerebrovascular disease. Calculation of a cardiovascular risk score may have aided in differentiating between the impact of vascular disease and autonomic dysfunction. However, the complete data required for this, including fasting lipids, were not collected as part of this study.

Orthostatic hypertension is known to be a risk factor for cardiovascular disease and can result in end organ damage including silent cerebrovascular disease (Kario 2013). Using brain magnetic resonance imaging (MRI) adults with orthostatic hypertension have been found to have more silent infarcts than controls (Eguchi *et al.* 2004). White matter changes and cerebral infarcts are associated with the development of post-operative delirium (Kant *et al.* 2017). One of the most common complications following symptomatic stroke is the development of delirium (McManus *et al.* 2007). Similar to the reverse dipping status, orthostatic hypertension in delirious participants could also relate to cerebrovascular disease.

5.4 Comparison to Autonomic Function in Dementia

Previous research has investigated for an association between dementia and various aspects of autonomic function. Given that dementia is a risk factor for the development of delirium (Fong *et al.* 2009) and patients who have had delirium are at higher risk of developing dementia (Davis *et al.* 2012), autonomic function abnormalities may be common to the two conditions.

Studies have reported an association between dementia and baroreceptor function (Meel-van den Abeelen *et al.* 2013; Saint Martin *et al.* 2013) and have identified reduced baroreflex sensitivity in participants with dementia. This is similar to the findings of this study. However, the above two studies did not subdivide baroreceptor sensitivity into up and down trends in bloods pressure, as was done in this study. It is therefore not possible to ascertain if the dementia studies found impairments related to excess or impaired sympathetic activity.

Another study (Mellingsæter *et al.* 2015) found a reduction in the sympathetic response to tilting in patients with Mild Cognitive Impairment or mild Alzheimer's

Dementia. This differs from the findings of this research with the tilt and baroreflex sensitivity tests suggesting either excess sympathetic activity or reduced parasympathetic activity in the delirious population.

A reverse nocturnal blood pressure dipping status has been associated with worse cognitive function as measured using the MoCA (Conway *et al.* 2015). Reduced nocturnal dipping in young adulthood is associated with lower executive function in midlife (Yano *et al.*). Our study also identified a reversed pattern in delirious participants. It is possible that the mechanisms that lead to cognitive deficits are common to both conditions and may be a marker of the underlying vascular disease associated with reverse blood pressure dipping.

The clinical implications of the above comparisons require further investigation. As impaired baroreflex sensitivity and a reverse nocturnal blood pressure pattern appear to be common to both conditions, further consideration should be given to ascertaining if these measures could be used to identify people who have had delirium and are at risk of developing future dementia.

5.5 Strengths of the Study

This is the first study to look for an association between autonomic impairment and delirium outside of the ICU setting. As delirium is very common in the general hospital population it is important to include this population in research.

This is the first study to look at autonomic function markers other than short term (15 minute) heart rate variability and to incorporate more than one component of autonomic function in the delirious population. This is important as heart rate

variability is only one component of autonomic function and important information may be missed by looking at it in isolation.

Delirium diagnosis was based on the DSM-IV criteria which is a delirium diagnostic rather than screening tool. The CAM-ICU is a screening tool commonly used in ICU studies as a means to identify delirium. This study also used the DRS-R98 which is a comprehensive assessment of delirium and allowed for delirium severity to be correlated to various autonomic tests, thereby allowing a 'dose-response' relationship to be evaluated.

Participants with pre-existing cognitive impairment were identified, thereby allowing the impact of this to be excluded. This is important because as discussed in Chapter 4 and Section 5.4 of this thesis, autonomic function differs in those with delirium and dementia.

Delirium subtype was characterised in this study. Although the sample size is not large enough to draw definite conclusions, the results do open the possibility that autonomic function may vary according to delirium subtype.

Autonomic function testing took place when participants were free of acute illness. This helped to minimise the impact that other acute conditions would have on the results.

The population enrolled in this study were largely an older, frailer population, which would reflect the population at greatest risk of developing delirium.

5.6 Weaknesses of the Study

This study is limited by the small sample. This may have led to a type 1 error in the Head-Up tilt test, baroreflex sensitivity, 24-hour blood pressure variability and diurnal blood pressure variability components of the study. Many results are however consistent throughout the study.

The small sample size may have also caused a type 2 error in the heart rate variability component of the study, suggesting no relationship when there truly is one.

Recruitment and follow up difficulties were encountered during the course of the study. This was largely due to the older age included, the high prevalence of frailty in the study population and the morbidity and mortality associated with delirium. The participants who did not attend follow-up had higher illness severity scores during their initial admission. The population included does however reflect the population at highest risk of developing delirium and it is important to include this group in any delirium research study.

Selection bias may have occurred by only including participants who were already under the care of a consultant geriatrician. Using this selection criterion ensured sufficient follow up of any abnormalities identified during the study, which is important for ethical reasons.

Delirium testing took place at one-time point only which may have led to participants being wrongly classified as not having delirium. In order to minimise this risk, the medical and nursing notes were reviewed for evidence of delirium and collateral histories taken from staff involved in the patient's care.

Although race was not included in the inclusion or exclusion criteria, all participants were recruited in Ireland and were Irish. This may limit the generalisability to other populations. No participants were in ICU or receiving end of life care. Delirium is very common in both of these settings but the results of this study may not apply to these patients.

Many of the limitations of the study are expected when studying a population with delirium. Despite these limitations this study provides a novel theory to explain the complex pathophysiology underlying an understudied topic.

5.7 Directions for Future Study

This study presents new hypotheses on which to base future research in delirium.

A larger study would be required to confirm the associations between sympathetic over-activity and delirium identified in this study. The results outlined in Chapter 4 were used to carry out post hoc sample size calculations that could be used to ensure sufficient power for future studies (Table 21).

Table 21: Post Hoc Sample Size Calculations

Autonomic Function Test	Number of Participants Required
Change in Systolic Blood Pressure on Head-Up Tilt	44
Supine Baroreflex Effectiveness Index	46
Erect Baroreflex Effectiveness Index	62
Low Frequency Heart Rate Variability	86
High Frequency Heart Rate Variability	132
Average Real Variability of Blood Pressure	114

Post hoc sample size calculations are based on a power of 80% and a two-sided significance level of 5%.

A similar study would however only have the potential to confirm an association between autonomic impairment and delirium. In order to ascertain if autonomic impairment is causative in the development of delirium, a longitudinal cohort study would be required. Participants with normal cognition and no history of delirium would need to be recruited, have autonomic function testing carried out at the onset of the study and be followed up for the future development of delirium or changes in autonomic function.

As outlined previously, some of the associations between autonomic impairment and delirium may relate to cerebrovascular disease. It is therefore important that future studies would have a measure of cerebrovascular disease included, such as magnetic resonance imaging of the brain.

The comparisons between hyperactive and hypoactive delirium provide a hypothesis that the clinical features of the different delirium subtypes may relate to autonomic function. Confirmation of this should be a focus of future research as it may identify different treatment targets for different subtypes. Targeting delirium treatment towards treatment of underlying autonomic dysfunction would however pose a challenge as current treatments are largely targeted at symptoms control. Equally, preventing the development of autonomic impairment is difficult due to the multitude of underlying causes.

Given the interrelationship between delirium and dementia, future studies of autonomic function should involve both conditions and attempt to identify if particular characteristics of autonomic function could be used to identify patients with delirium who are at risk of developing dementia.

This study encountered a number of issues with recruitment and follow-up. Future studies would likely also have these issues. Our syncope unit maintains a large

database of autonomic function tests carried out over several years. One potential method of reducing follow-up difficulties would be to retrospectively review the results of these tests and carry out a chart review to determine future development of delirium. Potential difficulties with this would however include the lack of standardised delirium diagnostic tools in clinical practice and compliance with the General Data Protection Regulation.

5.8 Conclusion

This thesis presented research that investigated for an association between delirium and autonomic impairment. This was a novel approach to attempting to identify the underlying pathophysiology of a common but poorly understood condition. The results of this study show that there is an association between delirium and autonomic impairment with differences detected between the delirium and control groups with regard to orthostatic blood pressure changes, baroreflex sensitivity, diurnal blood pressure variability and 24-hour blood pressure variability. The results differ from some of the findings of previous research investigating the relationship between dementia and autonomic impairment, suggesting differences in autonomic function in delirium and dementia. As one of the first studies of its kind, this study provides new hypotheses and opens the possibility for a range of future research opportunities.

References

Acharya, U.R., Joseph, K.P., Kannathal, N., Lim, C.M. and Suri, J.S. (2006) 'Heart rate variability: a review', *Medical and biological engineering and computing*, 44(12), 1031-1051.

Agarwal, A., Garg, R., Ritch, A. and Sarkar, P. (2007) 'Postural orthostatic tachycardia syndrome', *Postgraduate medical journal*, 83(981), 478-480.

Al-Aama, T., Brymer, C., Gutmanis, I., Woolmore-Goodwin, S.M., Esbaugh, J. and Dasgupta, M. (2011) 'Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial', *International journal of geriatric psychiatry*, 26(7), 687-694, available: http://dx.doi.org/10.1002/gps.2582.

Ali, S., Patel, M., Jabeen, S., Bailey, R.K., Patel, T., Shahid, M., Riley, W.J. and Arain, A. (2011) 'Insight into Delirium', *Innovations in Clinical Neuroscience*, 8(10), 25-34.

Amiya, E., Watanabe, M. and Komuro, I. (2014) 'The relationship between vascular function and the autonomic nervous system', *Annals of vascular diseases*, 7(2), 109.

Arthur, W. and Kaye, G. (2000) 'The pathophysiology of common causes of syncope', *Postgraduate medical journal*, 76(902), 750-753.

Attard, A., Ranjith, G. and Taylor, D. (2008) 'Delirium and its treatment', *CNS drugs*, 22(8), 631-644.

Bellelli, G., Morandi, A., Davis, D.H., Mazzola, P., Turco, R., Gentile, S., Ryan, T., Cash, H., Guerini, F. and Torpilliesi, T. (2014) 'Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people', *Age and ageing*, 43(4), 496-502.

Bittinger, M., Barnert, J. and Wienbeck, M. (1999) 'Autonomic dysfunction and the gastrointestinal tract', *Clinical Autonomic Research*, 9(2), 75-81.

Bolton, C., Thompson, J., Bernardi, L., Voll, C. and Young, B. (2007) 'The cardiac RR variation and sympathetic skin response in the intensive care unit', *The Canadian Journal of Neurological Sciences*, 34(03), 313-315.

Boorsma, M., Joling, K.J., Frijters, D.H., Ribbe, M.E., Nijpels, G. and Hout, H.P. (2012) 'The prevalence, incidence and risk factors for delirium in Dutch nursing homes and residential care homes', *International journal of geriatric psychiatry*, 27(7), 709-715.

Browning, K.N. and Travagli, R.A. (2011) 'Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions', Comprehensive physiology, 4(4), 1339-1368.

Bouch, D.C. and Thompson, J.P. (2008) 'Severity scoring systems in the critically ill', Continuing Education in Anaesthesia, Critical Care & Pain, 8(5), 181-185.

Buchman, T.G., Stein, P.K. and Goldstein, B. (2002) 'Heart rate variability in critical illness and critical care', *Current opinion in critical care*, 8(4), 311-315.

Burns, A., Gallagley, A. and Byrne, J. (2004) 'Delirium', *Journal of Neurology, Neurosurgery & Psychiatry*, 75(3), 362-367.

Calhoun, D.A. and Harding, S.M. (2010) 'Sleep and Hypertension', *Chest*, 138(2), 434-443, available: http://dx.doi.org/10.1378/chest.09-2954.

Castro-Diehl, C., Diez Roux, A.V., Redline, S., Seeman, T., McKinley, P., Sloan, R. and Shea, S. (2016) 'Sleep Duration and Quality in Relation to Autonomic Nervous System Measures: The Multi-Ethnic Study of Atherosclerosis (MESA)', *Sleep*, 39(11), 1927-1940, available: http://dx.doi.org/10.5665/sleep.6218.

Cavallazzi, R., Saad, M. and Marik, P.E. (2012) 'Delirium in the ICU: an overview', *Annals of Intensive Care*, 2(1), 1-11, available: http://dx.doi.org/10.1186/2110-5820-2-49.

Chakraborti, D., Tampi, D.J. and Tampi, R.R. (2015) 'Melatonin and melatonin agonist for delirium in the elderly patients', *American journal of Alzheimer's disease and other dementias*, 30(2), 119-129.

Chapple, C.R. (2005) 'A Comparison of Varying alpha-Blockers and Other Pharmacotherapy Options for Lower Urinary Tract Symptoms', *Reviews in urology*, 7 Suppl 4(Suppl 4), S22-S30.

Chhabra, L. and Spodick, D.H. (2013) 'Orthostatic hypertension: recognizing an underappreciated clinical condition', *Indian heart journal*, 65(4), 454-456, available: http://dx.doi.org/10.1016/j.ihj.2013.06.023.

Cipolla, M.J. (2009) 'Control of cerebral blood flow' in The cerebral circulation Morgan & Claypool Life Sciences.

Cooke, J., Carew, S., O'connor, M., Costelloe, A., Sheehy, T. and Lyons, D. (2009) 'Sitting and standing blood pressure measurements are not accurate for the diagnosis of orthostatic hypotension', *QJM: An International Journal of Medicine*, 102(5), 335-339.

Colkesen, Y., Giray, S., Ozenli, Y., Sezgin, N. and Coskun, I. 'Relation of serum cortisol to delirium occurring after acute coronary syndromes', *The American Journal of Emergency Medicine*, 31(1), 161-165, available: http://dx.doi.org/10.1016/j.ajem.2012.07.001.

Conway, K.S., Forbang, N., Beben, T., Criqui, M.H., Ix, J.H. and Rifkin, D.E. (2015) 'Relationship Between 24-Hour Ambulatory Blood Pressure and Cognitive Function in Community-Living Older Adults: The UCSD Ambulatory Blood Pressure Study', *American journal of hypertension*, 28(12), 1444-1452, available: http://dx.doi.org/10.1093/ajh/hpv042.

Cuspidi, C., Sala, C., Tadic, M., Gherbesi, E., De Giorgi, A., Grassi, G. and Mancia, G. (2017) 'Clinical and prognostic significance of a reverse dipping pattern on ambulatory monitoring: An updated review', *The Journal of Clinical Hypertension*, 19(7), 713-721.

Daly, D.D. (1980) 'Delirium: Acute Brain Failure in Man', *American Journal of Psychiatry*, 137(9), 1139-1139, available: http://dx.doi.org/10.1176/ajp.137.9.1139.

Davis, D.H.J., Muniz Terrera, G., Keage, H., Rahkonen, T., Oinas, M., Matthews, F.E., Cunningham, C., Polvikoski, T., Sulkava, R. and MacLullich, A.M.J. (2012) 'Delirium is a strong risk factor for dementia in the oldest-old: a population-based cohort study', *Brain*, 135(9), 2809-2816.

Donaghy, M. (2009) *Brain's Diseases of the Nervous System*, Oxford University Press; available:http://oxfordmedicine.com/view/10.1093/med/9780198569381.001.0001/med-9780198569381

Duby, J.J., Campbell, R.K., Setter, S.M. and Rasmussen, K. (2004) 'Diabetic neuropathy: an intensive review', *American Journal of Health-System Pharmacy*, 61(2), 160-173.

Eguchi, K., Kario, K., Hoshide, S., Hoshide, Y., Ishikawa, J., Morinari, M., Hashimoto, T. and Shimada, K. (2004) 'Greater change of orthostatic blood pressure is related to silent cerebral infarct and cardiac overload in hypertensive subjects', *Hypertension Research*, 27(4), 235-241.

ESC-Task Force of The European Society of Cardiology and The North American Society of Pacing and Electrophysiology. (1996) 'Heart rate variability standards of measurement, physiological interpretation, and clinical use', *Eur Heart J*, 17, 354-381.

Farley, A. and McLafferty, E. (2007) 'Delirium part one: clinical features, risk factors and assessment', *Nursing Standard*, 21(29), 35-40.

Figueroa, J.J., Basford, J.R. and Low, P.A. (2010) 'Preventing and treating orthostatic hypotension: as easy as A, B, C', *Cleveland Clinic journal of medicine*, 77(5), 298.

Flacker, J.M. and Lipsitz, L.A. (1999) 'Neural Mechanisms of Delirium: Current Hypotheses and Evolving Concepts', *Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences*, 54(6), B239-B246, available: http://dx.doi.org/10.1093/gerona/54.6.B239.

Fong, T., Jones, R., Shi, P., Marcantonio, E., Yap, L., Rudolph, J., Yang, F.M., Kiely, D. and Inouye, S. (2009) 'Delirium accelerates cognitive decline in Alzheimer disease', *Neurology*, 72(18), 1570-1575.

Fong, T.G., Bogardus Jr, S.T., Daftary, A., Auerbach, E., Blumenfeld, H., Modur, S., Leo-Summers, L., Seibyl, J. and Inouye, S.K. (2006) 'Cerebral perfusion changes in older delirious patients using 99mTc HMPAO SPECT', *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 61(12), 1294-1299.

Fong, T.G., Tulebaev, S.R. and Inouye, S.K. (2009) 'Delirium in elderly adults: diagnosis, prevention and treatment', *Nature Reviews Neurology*, 5(4), 210.

Fulton, B., Wagstaff, A.J. and Sorkin, E.M. (1995) 'Doxazosin', *Drugs*, 49(2), 295-320.

Giovannitti Jr, J.A., Thoms, S.M. and Crawford, J.J. (2015) 'Alpha-2 adrenergic receptor agonists: a review of current clinical applications', *Anesthesia progress*, 62(1), 31-38.

Goldstein, D.S. and Sharabi, Y. (2009) 'Neurogenic Orthostatic Hypotension A Pathophysiological Approach', *Circulation*, 119(1), 139-146.

Golinger, R.C. and Tune, L.E. (1987) 'Association of Elevated Plasma Anticholinergic Activity', *Am J Psychiatry*, 144, 1218-1220.

Gonzalez, M., Martinez, G., Calderon, J., Villarroel, L., Yuri, F., Rojas, C., Jeria, A., Valdivia, G., Marin, P.P. and Carrasco, M. (2009) 'Impact of delirium on short-term mortality in elderly inpatients: a prospective cohort study', *Psychosomatics*, 50(3), 234-8, available: http://dx.doi.org/10.1176/appi.psy.50.3.234.

Grubb, B.P. (2005) 'Neurocardiogenic syncope and related disorders of orthostatic intolerance', *Circulation*, 111(22), 2997-3006.

Guo, Z.-N., Xing, Y., Wang, S., Ma, H., Liu, J. and Yang, Y. (2015) 'Characteristics of dynamic cerebral autoregulation in cerebral small vessel disease: Diffuse and sustained', *Scientific reports*, 5.

Haggstrom, L., Welschinger, R. and Caplan, G.A. (2017) 'Functional neuroimaging offers insights into delirium pathophysiology: A systematic review', *Australasian Journal on Ageing*, 36(3), 186-192, available: http://dx.doi.org/10.1111/ajag.12417.

Halaas, N.B., Blennow, K., Idland, A.-V., Wyller, T.B., Ræder, J., Frihagen, F., Staff, A.C., Zetterberg, H. and Watne, L.O. (2018) 'Neurofilament Light in the Serum and Cerebrospinal Fluid of Hip Fracture Patients with Delirium', *Dementia and geriatric cognitive disorders*, 46(5-6), 346-357.

Hall, R.J., Davis, D., White, T.O., Armstrong, I., Seckl, J.R. and MacLullich, A.M.J. (2016) '55 Cortisol diiurnal rhythm and inflammation in delirium after hip fracture', *Age and Ageing*, 45(suppl_1), i17-i17, available: http://dx.doi.org/10.1093/ageing/afw032.02.

Höcht, C. (2013) 'Blood pressure variability: prognostic value and therapeutic implications', *ISRN Hypertension*, 2013.

Hov, K.R., Neerland, B.E., Andersen, A.M., Undseth, Ø., Wyller, V.B., MacLullich, A.M.J., Skovlund, E., Qvigstad, E. and Wyller, T.B. (2018) 'The use of clonidine in elderly patients with delirium; pharmacokinetics and hemodynamic responses', *BMC Pharmacology and Toxicology*, 19(1), 29.

Hu, K., Peng, C., Huang, N.E., Wu, Z., Lipsitz, L.A., Cavallerano, J. and Novak, V. (2008) 'Altered phase interactions between spontaneous blood pressure and flow fluctuations in type 2 diabetes mellitus: nonlinear assessment of cerebral autoregulation', *Physica A: Statistical Mechanics and its Applications*, 387(10), 2279-2292.

Hughes, C.G., Morandi, A., Girard, T.D., Riedel, B., Thompson, J.L., Shintani, A.K., Pun, B.T., Ely, E.W. and Pandharipande, P.P. (2013) 'Association between endothelial dysfunction and acute brain dysfunction during critical illness', *The Journal of the American Society of Anesthesiologists*, 118(3), 631–639-631–639.

Kant, I.M.J., de Bresser, J., van Montfort, S.J.T., Slooter, A.J.C. and Hendrikse, J. (2017) 'MRI Markers of Neurodegenerative and Neurovascular Changes in Relation to Postoperative Delirium and Postoperative Cognitive Decline', *The American Journal of Geriatric Psychiatry*, 25(10), 1048-1061, available: http://dx.doi.org/https://doi.org/10.1016/j.jagp.2017.06.016.

Kario, K. (2013) 'Orthostatic hypertension—a new haemodynamic cardiovascular risk factor', *Nature Reviews Nephrology*, 9, 726, available: http://dx.doi.org/10.1038/nrneph.2013.224.

Kasaoka, S., Nakahara, T., Kawamura, Y., Tsuruta, R. and Maekawa, T. (2010) 'Real-time monitoring of heart rate variability in critically ill patients', *Journal of critical care*, 25(2), 313-316.

Kaufmann, H., Norcliffe-Kaufmann, L. and Palma, J.-A. (2015) 'Droxidopa in neurogenic orthostatic hypotension', *Expert review of cardiovascular therapy*, 13(8), 875-891.

Kazmierski, J., Banys, A., Latek, J., Bourke, J. and Jaszewski, R. (2013) 'Cortisol levels and neuropsychiatric diagnosis as markers of postoperative delirium: a prospective cohort study', *Critical Care*, 17(2), R38-R38, available: http://dx.doi.org/10.1186/cc12548.

Khurana, R. and Setty, A. (1996) 'The value of the isometric hand-grip test-studies in various autonomic disorders', *Clinical Autonomic Research*, 6(4), 211-218.

Kougias, P., Weakley, S.M., Yao, Q., Lin, P.H. and Chen, C. (2010) 'Arterial baroreceptors in the management of systemic hypertension', *Medical science monitor: international medical journal of experimental and clinical research*, 16(1), RA1.

Kouidi, E., Haritonidis, K., Koutlianos, N. and Deligiannis, A. (2002) 'Effects of athletic training on heart rate variability triangular index', *Clinical physiology and functional imaging*, 22(4), 279-284.

Krausz, Y., Bonne, O., Gorfine, M., Karger, H., Lerer, B. and Chisin, R. (1998) 'Age-related changes in brain perfusion of normal subjects detected by 99mTc-HMPAO SPECT', *Neuroradiology*, 40(7), 428-434, available: http://dx.doi.org/10.1007/s002340050617.

Kukreja, D., Günther, U. and Popp, J. (2015) 'Delirium in the elderly: Current problems with increasing geriatric age', *The Indian journal of medical research*, 142(6), 655-662, available: http://dx.doi.org/10.4103/0971-5916.174546.

Kuo, B. and Urma, D. (2006) 'Esophagus-anatomy and development', *GI Motility online*. Available: doi:10.1038/gimo6

Kyziridis, T.C. (2006) 'Post-operative delirium after hip fracture treatment - a review of the current literature', *GMS Psycho-Social Medicine*, 3.

La Rovere, M.T., Pinna, G.D. and Raczak, G. (2008) 'Baroreflex sensitivity: measurement and clinical implications', Annals of noninvasive electrocardiology, 13(2), 191-207.

Lanier, J.B., Mote, M.B. and Clay, E.C. (2011) 'Evaluation and management of orthostatic hypotension', *American family physician*, 84(5).

Lee, K.F.H., Wood, M.D., Maslove, D.M., Muscedere, J.G. and Boyd, J.G. (2018) 'Dysfunctional cerebral autoregulation is associated with delirium in critically ill adults', *Journal of Cerebral Blood Flow & Metabolism*, 0271678X18803081.

Lewis, M.C. and Barnett, S.R. (2004) 'Postoperative delirium: the tryptophan dyregulation model', *Medical Hypotheses*, 63(3), 402-406, available: http://dx.doi.org/http://dx.doi.org/10.1016/j.mehy.2004.01.033.

Liptzin, B., Laki, A., Garb, J.L., Fingeroth, R. and Krushell, R. (2005) 'Donepezil in the prevention and treatment of post-surgical delirium', *The American journal of geriatric psychiatry*, 13(12), 1100-1106.

Lonergan, E., Luxenberg, J. and Areosa Sastre, A. (2009) 'Benzodiazepines for delirium', *The Cochrane Library*.

Lump, D. and Moyer, M. (2014) 'Paroxysmal sympathetic hyperactivity after severe brain injury', Curr Neurol Neurosci Rep 14(11), 494,available: https://doi.org/10.1007/s11910-014-0494-0

MacLullich, A.M.J., Ferguson, K.J., Miller, T., de Rooij, S.E.J.A. and Cunningham, C. (2008) 'Unravelling the pathophysiology of delirium: A focus on the role of aberrant stress responses', *Journal of Psychosomatic Research*, 65(3), 229-238,available: http://dx.doi.org/http://dx.doi.org/10.1016/j.jpsychores.2008.05.019.

Mancia, G. and Grassi, G. (2014) 'The autonomic nervous system and hypertension', *Circulation research*, 114(11), 1804-1814.

Marcantonio, E.R., Flacker, J.M., Michaels, M. and Resnick, N.M. (2000) 'Delirium is independently associated with poor functional recovery after hip fracture', *Journal of the American Geriatrics Society*, 48(6), 618-624.

Marcantonio, E.R., Ngo, L.H., O'Connor, M. and et al. (2014) '3d-cam: Derivation and validation of a 3-minute diagnostic interview for cam-defined delirium: a cross-sectional diagnostic test study', *Annals of Internal Medicine*, 161(8), 554-561, available: http://dx.doi.org/10.7326/M14-0865.

Marcantonio, E.R., Palihnich, K., Appleton, P. and Davis, R.B. (2011) 'Pilot randomized trial of donepezil hydrochloride for delirium after hip fracture', *Journal of the American Geriatrics Society*, 59, S282-S288.

Mathias, C.J. (2003) 'Autonomic diseases: clinical features and laboratory evaluation', *Journal of Neurology, Neurosurgery & Psychiatry*, 74(suppl 3), iii31-iii41.

McAinsh, J. and Cruickshank, J.M. (1990) 'Beta-blockers and central nervous system side effects', *Pharmacology & therapeutics*, 46(2), 163-197.

McCorry, L.K. (2007) 'Physiology of the autonomic nervous system', *American journal of pharmaceutical education*, 71(4).

McDougall, A.J. and McLeod, J.G. (1996) 'Autonomic neuropathy, I. Clinical features, investigation, pathophysiology, and treatment', *Journal of the neurological sciences*, 137(2), 79-88.

McGleenon, B.M., Dynan, K.B. and Passmore, A.P. (1999) 'Acetylcholinesterase inhibitors in Alzheimer's disease', *British journal of clinical pharmacology*, 48(4), 471.

McManus, J., Pathansali, R., Stewart, R., Macdonald, A. and Jackson, S. (2007) 'Delirium post-stroke', Age and Ageing, 36(6), 613-618.

Meagher, D. (2009) 'Motor subtypes of delirium: past, present and future', *International Review of Psychiatry*, 21(1), 59-73.

Meagher, D., Adamis, D., Leonard, M., Trzepacz, P., Grover, S., Jabbar, F., Meehan, K., O'Connor, M., Cronin, C., Reynolds, P., Fitzgerald, J., O'Regan, N., Timmons, S., Slor, C., de Jonghe, J., de Jonghe, A., van Munster, B.C., de Rooij, S.E. and Maclullich, A. (2014) 'Development of an abbreviated version of the Delirium Motor Subtyping Scale (DMSS-4)', *International Psychogeriatrics*, 26(4), 693-702, available: http://dx.doi.org/10.1017/S1041610213002585.

Meel-van den Abeelen, A.S.S., Lagro, J., Gommer, E.D., Reulen, J.P.H. and Claassen, J.A.H.R. (2013) 'Baroreflex function is reduced in Alzheimer's disease: a candidate biomarker?', *Neurobiology of Aging*, 34(4), 1170-1176, available: http://dx.doi.org/https://doi.org/10.1016/j.neurobiolaging.2012.10.010.

Mellingsæter, M.R., Wyller, T.B., Ranhoff, A.H., Bogdanovic, N. and Wyller, V.B. (2015) 'Reduced Sympathetic Response to Head-Up Tilt in Subjects with Mild Cognitive Impairment or Mild Alzheimer's Dementia', *Dementia and Geriatric*

Cognitive Disorders Extra, 5(1), 107-115, available: http://dx.doi.org/10.1159/000375297.

Mena, L.J., Felix, V.G., Melgarejo, J.D. and Maestre, G.E. (2017) '24-hour blood pressure variability assessed by average real variability: a systematic review and meta-analysis', Journal of the American Heart Association, 6(10), e006895.

Miao, S., Shen, P., Zhang, Q., Wang, H., Shen, J., Wang, G. and Lv, D. (2018) 'Neopterin and mini-mental state examination scores, two independent risk factors for postoperative delirium in elderly patients with open abdominal surgery', *Journal of cancer research and therapeutics*, 14(6), 1234.

Milazzo, V., Stefano, C.D., Servo, S., Crudo, V., Fulcheri, C. and Maule, S. (2012) 'Drugs and orthostatic hypotension: evidence from literature', *J Hypertens*, 1(104), 2167-1095.

Morrin, N.M., Stone, M.R. and Henderson, K.J. (2017) 'Reproducibility of 24-h ambulatory blood pressure and measures of autonomic function', *Blood pressure monitoring*, 22(3), 169-172.

Narkiewicz, K., Winnicki, M., Schroeder, K., Phillips, B.G., Kato, M., Cwalina, E. and Somers, V.K. (2002) 'Relationship Between Muscle Sympathetic Nerve Activity and Diurnal Blood Pressure Profile', *Hypertension*, 39(1), 168-172, available: http://dx.doi.org/10.1161/hy1201.097302.

National Institiude for Health and Care Excellence (NICE). (2010) ‘Delirium : prevention, diagnosis and management’, available at: https://www.nice.org.uk/guidance/cg103/chapter/1-Guidance

Neufeld, K.J., Yue, J., Robinson, T.N., Inouye, S.K. and Needham, D.M. (2016) 'Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis', *Journal of the American Geriatrics Society*, 64(4), 705-714.

Nielsen, S.E. and Mather, M. (2015) 'Comparison of two isometric handgrip protocols on sympathetic arousal in women', *Physiology & behavior*, 142, 5-13.

Novak, P. (2011) 'Quantitative autonomic testing', *JoVE (Journal of Visualized Experiments)*, (53), e2502-e2502.

Novak, V., Novak, P., Spies, J.M. and Low, P.A. (1998) 'Autoregulation of cerebral blood flow in orthostatic hypotension', *Stroke*, 29(1), 104-111, available: http://dx.doi.org/10.1161/01.STR.29.1.104.

O'Neal, J.B., Billings Iv, F.T., Liu, X., Shotwell, M.S., Liang, Y., Shah, A.S., Ehrenfeld, J.M., Wanderer, J.P. and Shaw, A.D. (2017) 'Effect of preoperative beta-blocker use on outcomes following cardiac surgery', *The American journal of cardiology*, 120(8), 1293-1297.

O'Regan, N.A., Ryan, D.J., Boland, E., Connolly, W., McGlade, C., Leonard, M., Clare, J., Eustace, J.A., Meagher, D. and Timmons, S. (2014) 'Attention! A good bedside test for delirium?', *Journal of Neurology, Neurosurgery & Psychiatry*, 85(10), 1122.

Ochodnicky, P., Uvelius, B., Andersson, K.E. and Michel, M. (2013) 'Autonomic nervous control of the urinary bladder', *Acta Physiologica*, 207(1), 16-33.

Oh, J., Cho, D., Park, J., Na, S.H., Kim, J., Heo, J., Shin, C.S., Kim, J.-J., Park, J.Y. and Lee, B. (2018) 'Prediction and early detection of delirium in the intensive care unit by using heart rate variability and machine learning', *Physiological measurement*, 39(3), 035004.

Ohta, T., Murao, K., Miyake, K. and Takemoto, K. (2013) 'Melatonin Receptor Agonists for Treating Delirium in Elderly Patients with Acute Stroke', *Journal of Stroke and Cerebrovascular Diseases*, 22(7), 1107-1110, available: http://dx.doi.org/http://dx.doi.org/10.1016/j.jstrokecerebrovasdis.2012.08.012.

Pandharipande, P., Morandi, A., Adams, J., Girard, T., Thompson, J., Shintani, A. and Ely, E.W. (2009) 'Plasma tryptophan and tyrosine levels are independent risk factors for delirium in critically ill patients', *Intensive care medicine*, 35(11),

Pandharipande, P.P., Pun, B.T., Herr, D.L., Maze, M., Girard, T.D., Miller, R.R., Shintani, A.K., Thompson, J.L., Jackson, J.C. and Deppen, S.A. (2007) 'Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial', *Jama*, 298(22), 2644-2653.

Paris, G., Gourcerol, G. and Leroi, A. (2011) 'Management of neurogenic bowel dysfunction', *European journal of physical and rehabilitation medicine*, 47(4), 661-676.

Parkes, L.M., Rashid, W., Chard, D.T. and Tofts, P.S. (2004) 'Normal cerebral perfusion measurements using arterial spin labeling: Reproducibility, stability, and age and gender effects', *Magnetic Resonance in Medicine*, 51(4), 736-743, available: http://dx.doi.org/10.1002/mrm.20023.

Pearson, A., de Vries, A., Middleton, S.D., Gillies, F., White, T.O., Armstrong, I.R., Andrew, R., Seckl, J.R. and MacLullich, A.M. (2010) 'Cerebrospinal fluid cortisol levels are higher in patients with delirium versus controls', *BMC Research Notes*, 3(1), 1-5, available: http://dx.doi.org/10.1186/1756-0500-3-33.

Peltola, M.A. (2007) 'Role of editing of R–R intervals in the analysis of heart rate variability', *Heart Rate Variability: Clinical Applications and Interaction between HRV and Heart Rate*, 29.

Pierdomenico, S.D., Di Nicola, M., Esposito, A.L., Di Mascio, R., Ballone, E., Lapenna, D. and Cuccurullo, F. (2009) 'Prognostic value of different indices of blood pressure variability in hypertensive patients', American journal of hypertension, 22(8), 842-847.

Protheroe, C.L., Dikareva, A., Menon, C. and Claydon, V.E. (2011) 'Are compression stockings an effective treatment for orthostatic presyncope?', *PloS one*, 6(12), e28193.

Quinn, T.J., Langhorne, P. and Stott, D.J. (2011) 'Barthel index for stroke trials: development, properties, and application', *Stroke*, 42(4), 1146-1151.

Ramirez-Bermudez, J., Ruiz-Chow, A., Perez-Neri, I., Soto-Hernandez, J.L., Flores-Hernandez, R., Nente, F., Montes, S. and Rios, C. (2008) 'Cerebrospinal fluid homovanillic acid is correlated to psychotic features in neurological patients with delirium', *General hospital psychiatry*, 30(4), 337-343.

Razavi, M., Tolea, M.I., Margrett, J., Martin, P., Oakland, A., Tscholl, D.W., Ghods, S., Mina, M. and Galvin, J.E. (2014) 'Comparison of Two Informant Questionnaire Screening Tools for Dementia and Mild Cognitive Impairment: AD8 and IQCODE', *Alzheimer disease and associated disorders*, 28(2), 156-161, available: http://dx.doi.org/10.1097/WAD.0000000000000008.

Revenig, L., Leung, A. and Hsiao, W. (2014) 'Ejaculatory physiology and pathophysiology: assessment and treatment in male infertility', *Translational Andrology and Urology*, 3(1), 41-49, available: http://dx.doi.org/10.3978/j.issn.2223-4683.2014.02.02.

Riker, R.R., Shehabi, Y., Bokesch, P.M., Ceraso, D., Wisemandle, W., Koura, F., Whitten, P., Margolis, B.D., Byrne, D.W. and Ely, E.W. (2009) 'Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial', *Jama*, 301(5), 489-499.

Ritchie, C.W., Newman, T.H., Leurent, B. and Sampson, E.L. (2014) 'The association between C-reactive protein and delirium in 710 acute elderly hospital admissions', *International Psychogeriatrics*, 26(05), 717-724, available: http://dx.doi.org/doi:10.1017/S1041610213002433.

Robinson, T.N., Raeburn, C.D., Angles, E.M. and Moss, M. (2008) 'Low tryptophan levels are associated with postoperative delirium in the elderly', *The American Journal of Surgery*, 196(5), 670-674.

Roffman, C.E., Buchanan, J. and Allison, G.T. (2016) 'Charlson Comorbidities Index', *Journal of Physiotherapy*, 62(3), 171, available: http://dx.doi.org/10.1016/j.jphys.2016.05.008.

Ryan, D.J., O'Regan, N.A., Caoimh, R.O., Clare, J., O'Connor, M., Leonard, M., McFarland, J., Tighe, S., O'Sullivan, K., Trzepacz, P.T., Meagher, D. and Timmons, S. (2013) 'Delirium in an adult acute hospital population: predictors, prevalence and detection', *BMJ Open*, 3(1), available: http://dx.doi.org/10.1136/bmjopen-2012-001772.

Saint Martin, M., Sforza, E., Thomas-Anterion, C., Barthélémy, J.C., Roche, F. and Group, P.S. (2013) 'Baroreflex sensitivity, vascular risk factors, and cognitive function in a healthy elderly population: the PROOF cohort', *Journal of the American Geriatrics Society*, 61(12), 2096-2102.

Sampson, E.L., Raven, P.R., Ndhlovu, P.N., Vallance, A., Garlick, N., Watts, J., Blanchard, M.R., Bruce, A., Blizard, R. and Ritchie, C.W. (2007) 'A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement', *International Journal of Geriatric Psychiatry: A journal of the psychiatry of late life and allied sciences*, 22(4), 343-349.

Saxena, S. and Lawley, D. (2009) 'Delirium in the elderly: a clinical review', *Postgraduate medical journal*, 85(1006), 405-413.

Schachter, M. (1999) 'Moxonidine: a review of safety and tolerability after seven years of clinical experience', *Journal of hypertension. Supplement: official journal of the International Society of Hypertension*, 17(3), S37-9.

Scott-Warren, V. and Sebastian, J. (2015) 'Dexmedetomidine: its use in intensive care medicine and anaesthesia', *BJA Education*, 16(7), 242-246, available: http://dx.doi.org/10.1093/bjaed/mkv047.

Scully, C. and Felix, D.H. (2005) '3: Oral Medicine [mdash] Update for the dental practitioner: Dry mouth and disorders of salivation', *Br Dent J*, 199(7), 423-427.

Seaman, J.S., Schillerstrom, J., Carroll, D. and Brown, T.M. (2006) 'Impaired oxidative metabolism precipitates delirium: a study of 101 ICU patients', *Psychosomatics*, 47(1), 56-61.

Searle, S.D., Mitnitski, A., Gahbauer, E.A., Gill, T.M. and Rockwood, K. (2008) 'A standard procedure for creating a frailty index', *BMC Geriatrics*, 8(1), 24, available: http://dx.doi.org/10.1186/1471-2318-8-24.

Sherwood, A., Steffen Pr Fau - Blumenthal, J.A., Blumenthal Ja Fau - Kuhn, C., Kuhn C Fau - Hinderliter, A.L. and Hinderliter, A.L. 'Nighttime blood pressure dipping: the role of the sympathetic nervous system', (0895-7061 (Print)).

Siddiqi, N., House, A.O. and Holmes, J.D. (2006) 'Occurrence and outcome of delirium in medical in-patients: a systematic literature review', *Age and Ageing*, 35(4), 350-364, available: http://dx.doi.org/10.1093/ageing/afl005.

Siepe, M., Pfeiffer, T., Gieringer, A., Zemann, S., Benk, C., Schlensak, C. and Beyersdorf, F. (2011) 'Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium', *Eur J Cardiothorac Surg*, 40(1), 200-7, available: http://dx.doi.org/10.1016/j.ejcts.2010.11.024.

Singer, W., Sandroni, P., Opfer-Gehrking, T.L., Suarez, G.A., Klein, C.M., Hines, S., O'Brien, P.C., Slezak, J. and Low, P.A. (2006) 'Pyridostigmine treatment trial in neurogenic orthostatic hypotension', *Arch Neurol*, 63(4), 513-8, available: http://dx.doi.org/10.1001/archneur.63.4.noc50340.

Skrobik, Y., Duprey, M.S., Hill, N.S. and Devlin, J.W. (2018) 'Low-dose nocturnal dexmedetomidine prevents ICU delirium. A randomized, placebo-controlled trial', *American Journal of Respiratory and Critical Care Medicine*, 197(9), 1147-1156.

Skullerud, K. (1985) 'Variations in the size of the human brain. Influence of age, sex, body length, body mass index, alcoholism, Alzheimer changes, and cerebral atherosclerosis', *Acta neurologica Scandinavica. Supplementum*, 102, 1-94.

Smith, P.J., Blumenthal, J.A., Hoffman, B.M., Rivelli, S., Palmer, S.M., Davis, R. and Mathew, J. (2016) 'Reduced Cerebral Perfusion Pressure Worsens Delirium Outcomes Following Lung Transplantation', *Annals of the American Thoracic Society*, 13(2), 180-187.

Snell, R.S. (2010) *Clinical Neuroanatomy*, Wolters Kluwer Health/Lippincott Williams & Wilkins.

Sztajzel, J. (2004) 'Heart rate variability: a noninvasive electrocardiographic method to measure the autonomic nervous system', *Swiss Med Wkly*, 134(35-36), 514-22, available: http://dx.doi.org/2004/35/smw-10321.

Tameem, A. and Krovvidi, H. (2013) 'Cerebral physiology', *Continuing Education in Anaesthesia Critical Care & Pain*, 13(4), 113-118, available: http://dx.doi.org/https://doi.org/10.1093/bjaceaccp/mkt001.

Tarvainen, M.P., Niskanen, J.-P., Lipponen, J.A., Ranta-aho, P.O. and Karjalainen, P.A. (2014) 'Kubios HRV – Heart rate variability analysis software', *Computer Methods and Programs in Biomedicine*, 113(1), 210-220, available: http://dx.doi.org/https://doi.org/10.1016/j.cmpb.2013.07.024.

Trzepacz, P.T., Mittal, D., Torres, R., Kanary, K., Norton, J. and Jimerson, N. (2001) 'Validation of the Delirium Rating Scale-revised-98: comparison with the delirium rating scale and the cognitive test for delirium', *The Journal of neuropsychiatry and clinical neurosciences*, 13(2), 229-242.

Tse, L., Schwarz, S.K.W., Bowering, J.B., Moore, R.L. and Barr, A.M. (2015) 'Incidence of and risk factors for delirium after cardiac surgery at a quaternary care center: a retrospective cohort study', *Journal of Cardiothoracic and Vascular Anesthesia*, 29(6), 1472-1479.

Tsioufis, C., Andrikou, I., Thomopoulos, C., Syrseloudis, D., Stergiou, G. and Stefanadis, C. (2011) 'Increased nighttime blood pressure or nondipping profile for prediction of cardiovascular outcomes', *Journal of human hypertension*, 25(5), 281.

Tune, L., Holland, A., Folstein, M., Damlouji, N., Gardner, T. and Coyle, J. (1981) 'Association of postoperative delirium with raised serum levels of anticholinergic drugs', *The Lancet*, 318(8248), 651-653.

van der Cammen, T.J., Tiemeier, H., Engelhart, M.J. and Fekkes, D. (2006) 'Abnormal neurotransmitter metabolite levels in Alzheimer patients with a delirium', *International journal of geriatric psychiatry*, 21(9), 838-843.

Van Eijk, M., Roes, K.C., Honing, M., Kuiper, M.A., Karakus, A., Van der JAgt, M., Spronk, P.E., Van Gool, W.A., Van der Mast, R.C. and Kesecioglu, J. (2011) 'Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial', *Critical Care*, 15(1), 1.

van Munster, B.C. Bisschop, P.H., Zwinderman, A.H., Korevaar, J.C., Endert, E., Wiersinga, W.J., van Oosten, H.E., Goslings, J.C. and De Rooij, S.E.J.A. (2010) 'Cortisol, interleukins and S100B in delirium in the elderly', *Brain and cognition*, 74(1), 18-23.

van Munster, B.C. and de Rooij, S. (2014) 'Delirium: a synthesis of current knowledge', *Clinical Medicine*, 14(2), 192-195.

Wagner, D.P. and Draper, E.A. (1984) 'Acute physiology and chronic health evaluation (APACHE II) and Medicare reimbursement', *Health care financing review*, Suppl(Suppl), 91-105.

Wagner, M., Jurcoane, A., Volz, S., Magerkurth, J., Zanella, F.E., Neumann-Haefelin, T., Deichmann, R., Singer, O.C. and Hattingen, E. (2012) 'Age-related changes of cerebral autoregulation: new insights with quantitative T2'-mapping and pulsed arterial spin-labeling MR imaging', *AJNR Am J Neuroradiol*, 33(11), 2081-7, available: http://dx.doi.org/10.3174/ajnr.A3138.

Walhovd, K.B., Westlye, L.T., Amlien, I., Espeseth, T., Reinvang, I., Raz, N., Agartz, I., Salat, D.H., Greve, D.N. and Fischl, B. (2011) 'Consistent neuroanatomical age-related volume differences across multiple samples', *Neurobiology of aging*, 32(5), 916-932.

Wei, L.A., Fearing, M.A., Sternberg, E.J. and Inouye, S.K. (2008) 'The Confusion Assessment Method: A Systematic Review of Current Usage', *Journal of the American Geriatrics Society*, 56(5), 823-830, available: http://dx.doi.org/10.1111/j.1532-5415.2008.01674.x.

Winge, K., Rasmussen, D. and Werdelin, L. (2003) 'Constipation in neurological diseases', *Journal of neurology, neurosurgery, and psychiatry*, 74(1), 13.

Wirch, J.L., Wolfe, L.A., Weissgerber, T.L. and Davies, G.A. (2006) 'Cold pressor test protocol to evaluate cardiac autonomic function', *Applied physiology, nutrition, and metabolism*, 31(3), 235-243.

Witlox, J., Eurelings, L.M., de Jonghe, J.M., Kalisvaart, K.J., Eikelenboom, P. and van Gool, W.A. (2010) 'Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: A meta-analysis', *JAMA*, 304(4), 443-451, available: http://dx.doi.org/10.1001/jama.2010.1013.

Yano, Y., Ning, H., Muntner, P., Reis, J.P., Calhoun, D.A., Viera, A.J., Levine, D.A., Jacobs, J.D.R., Shimbo, D., Liu, K., Greenland, P. and Lloyd-Jones, D. 'Nocturnal Blood Pressure in Young Adults and Cognitive Function in Midlife: The Coronary Artery Risk Development in Young Adults (CARDIA) Study'. *American journal of hypertension*, 28(10), 1240-1247.

Yokota, H., Ogawa, S., Kurokawa, A. and Yamamoto, Y. (2003) 'Regional cerebral blood flow in delirium patients', *Psychiatry and clinical neurosciences*, 57(3), 337-339.

Youde, J., Panerai, R., Gillies, C. and Potter, J. (2003) 'Reproducibility of circulatory changes to head-up tilt in healthy elderly subjects', *Age and Ageing*, 32(4), 375-381.

Zaal, I.J., Van Der Kooi, A.W., van Schelven, L.J., Oey, P.L. and Slooter, A.J. (2014) 'Heart rate variability in intensive care unit patients with delirium', *The Journal of neuropsychiatry and clinical neurosciences*, 27(2), e112-e116.

Zhang, J. (2007) 'Effect of age and sex on heart rate variability in healthy subjects', *Journal of manipulative and physiological therapeutics*, 30(5), 374-379.

Ziegler, D., Haxhiu, M.A., Kaan, E.C., Papp, J.G. and Ernsberger, P. (1996) 'Pharmacology of moxonidine, an I 1-imidazoline receptor agonist', *J Cardiovasc Pharmacol*, 27(suppl 3), S26-S37.

Zygmunt, A. and Stanczyk, J. (2010) 'Methods of evaluation of autonomic nervous system function', *Archives of Medical Science : AMS*, 6(1), 11-18, available: http://dx.doi.org/10.5114/aoms.2010.13500.

Appendices

Appendix A: Patient Consent Form

Investigating the Relationship between Autonomic Dysfunction, Delirium and Sarcopenia

If you wish to take part in this study please ensure that you have read the information leaflet that you were given. When you are satisfied that you understand the leaflet, what the study entails and that all your questions have been answered please proceed to complete this form which gives your permission take part in this study.

Please tick that you have read and agree with the following:

I understand the information presented in the information leaflet	Yes □	No □
All my questions have been satisfactorily answered	Yes □	No □
I understand that participation in the study is voluntary and can be withdrawn at any time	Yes □	No □
I agree for my medical notes to be reviewed for necessary information such as my past medical history and medications	Yes □	No □
I give permission for an anonymized version of my test results to be recorded and used for the purposes of the study	Yes □	No □
I understand that a record of the necessary results will be recorded in my medical notes and my GP or consultant may be informed of the results	Yes □	No □
I agree to participate in this study	Yes □	No □

Participants Name: _____

Signature of Participant:_____
Date:_____

Signature of Investigator:_____
Date:_____

Appendix B: Family Member Consent Form

Investigating the Relationship between Autonomic Dysfunction, Delirium and Sarcopenia

If you wish for your family member to take part in this study, please ensure that you have read the information leaflet that you were given. When you are satisfied that you understand the leaflet, what the study entails and that all your questions have been answered please proceed to complete this form which gives your permission for your family member to take part in this study.

Please tick that you have read and agree with the following:

I understand the information presented in the information leaflet	Yes □	No □
All my questions have been satisfactorily answered	Yes □	No □
I understand that participation in the study is voluntary and can be withdrawn at any time	Yes □	No □
I agree for my family member's medical notes to be reviewed for necessary information such as their past medical history and medications	Yes □	No □
I give permission for an anonymized version of the test results to be recorded and used for the purposes of the study	Yes □	No □
I understand that a record of the necessary results will be recorded in their medical notes and their GP or consultant may be informed of the results	Yes □	No □
I agree to my family member participating in this study	Yes □	No □

Participants Name: _____

Family Members Name:_____

Relationship to Participant:_____

Signature of Family Member:_____
Date:_____

Signature of Investigator:_____
Date:_____

Appendix C: Patient and Family Information Sheet

Investigating the Relationship between Autonomic Dysfunction, Delirium and Sarcopenia

Introduction

Delirium is a condition characterised by acute confusion, poor attention and a change in alertness. It is very common in older people admitted to hospital. It can occur in a number of conditions including infection, constipation or a change in medications. However the underlying mechanism by which it occurs is not understood. A medical study is currently being carried out in this hospital to investigate for possible mechanisms.

In order for any organ to function correctly it must have sufficient blood flow. The blood flow to the brain is controlled in part by part of the nervous system called the Autonomic Nervous System. We want to investigate if dysfunction in this system could be associated with delirium.

Sarcopenia is a condition where the body loses muscle mass. It is more common as a person gets older. Previous research has shown that it is associated with dementia. We want to investigate if it is associated with delirium.

Procedures

Patients who take part in the study will have the presence or absence of delirium confirmed using a set of memory tests. A family member will be contacted to ask about any previous confusion or memory problems. The results of these tests will be recorded in the participant's medical notes. Any tests carried out by your consultant as part of your routine care and any diagnosis made will be recorded for the study.

All participants will be asked to attend for an outpatient appointment after discharge. The memory tests will be repeated. The Autonomic Nervous System will be tested by using standard tests for this purpose- a 24 hour blood pressure monitor, a 24 hour heart monitor (holter) and a tilt table test that tests the heart rate and blood pressure response to changes in posture. The heart and blood pressure monitor are worn home and returned by a family member the following day. To look at body muscle mass a scan called a whole body DEXA scan will be carried. This does not involve exposure to any more radiation than is in the environment.

Participants may be asked to attend for further follow up if required.

Taking part in this study will not affect the treatment and investigations that participants would otherwise receive from medical and nursing staff.

Benefits

All participants will be checked for the presence of delirium. If detected this will allow the medical staff looking after you to adequately treat it.

All participants will have a thorough evaluation of memory function, blood pressure and heart rhythm and might not otherwise be carried out.

Participating in this study will help to further medical knowledge and may help to treat future patients with delirium.

Risks

People with delirium can sometimes become agitated if presented with a task they find difficult. If this occurs the test will be stopped.

The blood pressure monitor can be tight on your arm and some people find it hard to sleep because of it. It can be removed at home if necessary.

Exclusion from Participation

- Participants under the age of 65 are less likely to have delirium and are therefore excluded
- Patients with confusion due to alcohol or substance withdrawal as the underlying mechanism of delirium may be different
- Uncontrolled depression or recent stroke, heart attack or brain tumour as this may affect the results
- Unable to comply with the tests
- Patients whose consultant feels they are too sick to take part

Confidentiality

All personal information is confidential. Your name will not be attached to any data. All participants' names will be written in a log book and matched with an identification code. The log book will be stored in a secure location. The

identification code will be used on all assessment sheets. All data will be stored in a secure location. A copy of the assessment will be recorded in the participant's medical notes.

Compensation

This study is a non-profit study and we are therefore unable to provide any financial compensation to participants.

Voluntary Participation and Stopping the Study

All participation in the study is on a voluntary basis and will only be done with permission from the participant or their next-of-kin if they are unable to give permission themselves. Refusal to participate will not affect the level of care received. Participation in the study can be withdrawn at any time if you no longer wish for you/your family member to continue.

Permission

You will be asked to sign a form to state that you give permission for you/your family member to take part in this study. This includes permission for an anonymized version of your test results to be used as part of the study. If you are giving permission on behalf of your family member you are asked to give this leaflet to them when they are better. Permission can then be withdrawn if they wish.

Complaints Procedure

If you have any concerns or complaints regarding this study you may contact the researcher below.

Contact Information

If you have any queries you may contact the researcher:

Dr. Elaine Shanahan

Clinical Age Assessment Unit

University Hospital Limerick

elaine.shanahan1@hse.ie

Appendix D: Delirium Rating Scale Revised 1998 (DRS-R98)

SEVERITY SCALE

1. **Sleep-wake cycle disturbance**

Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses' reports, and patient. Try to distinguish sleep from resting with eyes closed.

0	not present
1	mild sleep continuity disturbance at night or occasional drowsiness during the day
2	moderate disorganization of sleep-wake cycle (eg, falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioral changes or very little nighttime sleep)
3	severe disruption of sleep-wake cycle (eg, day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness).

2. Perceptual disturbances and hallucinations

Illusions and hallucinations can be of any sensory modality. Misperceptions are "simple" if they are uncomplicated, such as a sound, noise, color, spot, or flashes and "complex" if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

0	Not present
1	mild perceptual disturbances (eg, feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)
2	illusions present
3	hallucinations present

3. Delusions

0	Not present
1	mildly suspicious, hypervigilant, or preoccupied
2	unusual or overvalued ideation that does not reach delusional proportions or could be plausible
3	delusional

Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient's usual cultural or religious background.

4. Lability of affect

Rate the patient's affect as the outward presentation of emotions and not as a description of what the patient feels.

0	Not present
1	affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
2	affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others
3	severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. Language

Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assess fluency, grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

0	Normal language
1	Mild impairment including word-finding difficulty or problems with naming or fluency
2	Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)
3	Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

6. Thought process abnormalities

Rate abnormalities of thinking processes based on verbal or written output. If a patient does not speak or write, do not rate this item.

0	Normal thought processes
1	Tangential or circumstantial
2	Associations loosely connected occasionally, but largely comprehensible
3	Associations loosely connected most of the time

7. Motor agitation

Rate by observation, including from other sources of observation such as by visitors, family and clinical staff. Do not include dyskinesia, tics, or chorea.

0	No restlessness or agitation
1	Mild restlessness of gross motor movements or mild fidgetiness.
2	Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.
3	Severe motor agitation, such as combativeness or a need for restraints or seclusion.

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8. Motor retardation

Rate movements by direct observation or from other sources of observation such as family, visitors, or clinical staff. Do not rate components of retardation that are caused by parkinsonian symptoms. Do not rate drowsiness or sleep.

0	No slowness of voluntary movements
1	Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment.
2	Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care.
3	Severe motor retardation with few spontaneous movements.

9. Orientation

Patients who cannot speak can be given a visual or auditory presentation of multiple choice answers. Allow patient to be wrong by up to 7 days instead of 2 days for patients hospitalized more than 3 weeks. Disorientation to person means not recognizing familiar persons and may be intact even if the person has naming difficulty but recognizes the person. Disorientation to person is most severe when one doesn't know one's own identity and is rare. Disorientation to person usually occurs after disorientation to time and/or place.

0	Oriented to person, place and time.
1	Disoriented to time (eg, by more than 2 days or wrong month or wrong year) or to place (eg, name of building, city, state), but not both
2	Disoriented to time and place
3	Disoriented to person

10. Attention

Patients with sensory deficits or who are intubated or whose hand movements are constrained should be tested using an alternate modality besides writing. Attention can be assessed during the interview (eg, verbal perseverations, distractibility, and difficulty with set shifting) and/or through use of specific tests, eg, digit span.

0	Alert and attentive.
1	Mildly distractible or mild difficulty sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses.
2	Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish the task.
3	Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment.

11. Short-term memory

Defined as recall of information (eg, 3 items presented either verbally or visually) after a delay of about 2 to 3 minutes. When formally tested, information must be registered adequately before recall is tested. The number of trials to register as well as effect of cueing can be noted on scoresheet. Patient should not be allowed to rehearse during the delay period and should be distracted during that time. Patient may speak or nonverbally communicate to the examiner the identity of the correct items. Short-term deficits noticed during the course of the interview can be used also.

0	Short-term memory intact.
1	Recalls 2/3 items; may be able to recall third item after category cueing.
2	Recalls 1/3 items; may be able to recall other items after category cueing.
3	Recalls 0/3 items.

12. Long-term memory

Can be assessed formally or through interviewing for recall of past personal (eg, past medical history or information or experiences that can be corroborated from another source) or general information that is culturally relevant. When formally tested, use a verbal and/or visual modality for 3 items that are adequately registered and recalled after at least 5 minutes. The patient should not be allowed to rehearse during the delay period during formal testing. Make allowances for patients with less than 8 years of education or who are mentally retarded regarding general information questions. Rating of the severity of deficits may involve a judgement about all the ways long-term memory is assessed, including recent and/or remote long-term memory ability informally tested during the interview as well as any formal testing of recent long-term memory using 3 items.

0	No significant long-term memory deficits
1	Recalls 2/3 items and/or has minor difficulty recalling details of other long-term information
2	Recalls 1/3 items and/or has moderate difficulty recalling other long-term information
3	Recalls 0/3 items and/or has severe difficulty recalling other long-term information

13. Visuospatial ability

Assess informally and formally. Consider patient's difficulty navigating one's way around living areas or environment (eg, getting lost). Test formally by drawing or copying a design, by arranging puzzle pieces, or by drawing a map and identifying major cities, etc. Take into account any visual impairments that may affect performance.

0	No impairment
1	Mild impairment such that overall design and most details or pieces are correct; and/or little difficulty navigating in his/her surroundings
2	Moderate impairment with distorted appreciation of overall design and/or several errors of details or pieces; and/or needing repeated redirection to keep from getting lost in a newer environment despite, trouble locating familiar objects in immediate environment
3	Severe impairment on formal testing; and/or repeated wandering or getting lost in environment

DRS-R98 DIAGNOSTIC ITEMS

These three items can be used to assist in the differentiation of delirium from other disorders for diagnostic and research purposes. They are added to the severity score for the total scale score, but are NOT included in the severity score.

14. Temporal onset of symptoms

Rate the acuteness of onset of the initial symptoms of the disorder or episode being currently assessed, not their total duration. Distinguish the onset of symptoms attributable to delirium when it occurs concurrently with a different preexisting psychiatric disorder. For example, if a patient with major depression is rated during a delirium episode due to an overdose, then rate the onset of the delirium symptoms.

0	no significant change from usual or longstanding baseline behavior
1	gradual onset of symptoms, occurring over a period of several weeks to a month
2	acute change in behavior or personality occurring over days to a week
3	abrupt change in behavior occurring over a period of several hours to a day

15. Fluctuation of symptom severity

Rate the waxing and waning of an individual or cluster of symptom(s) over the time frame being rated. Usually applies to cognition, affect, intensity of hallucinations, thought disorder, language disturbance. Take into consideration that perceptual disturbances usually occur intermittently, but might cluster in period of greater intensity when other symptoms fluctuate in severity.

0	no symptom fluctuation
1	symptom intensity fluctuates in severity over hours
2	symptom intensity fluctuates in severity over minutes

16. Physical disorder

Rate the degree to which a physiological, medical or pharmacological problem can be specifically attributed to have caused the symptoms being assessed. Many patients have such problems but they may or may not have causal relationship to the symptoms being rated.

0	none present or active
1	presence of any physical disorder that might affect mental state
2	drug, infection, metabolic disorder, CNS lesion or other medical problem that specifically can be implicated in causing the altered behavior or mental state

Appendix E: Eight-item Informant Interview to Differentiate Aging and Dementia (AD8)

Remember, "Yes, a change" indicates that there has been a change in the last several years caused by cognitive (thinking and memory) problems.	**YES, A change**	**NO, No change**	**N/A, Don't know**
1. Problems with judgment (e.g., problems making decisions, bad financial decisions, problems with thinking)			
2. Less interest in hobbies/activities			
3. Repeats the same things over and over (questions, stories, or statements)			
4. Trouble learning how to use a tool, appliance, or gadget (e.g., VCR, computer, microwave, remote control)			
5. Forgets correct month or year			
6. Trouble handling complicated financial affairs (e.g., balancing checkbook, income taxes, paying bills)			
7. Trouble remembering appointments			
8. Daily problems with thinking and/or memory			
TOTAL AD8 SCORE			

The AD8 Administration and Scoring Guidelines

A spontaneous self-correction is allowed for all responses without counting as an error.

The questions are given to the respondent on a clipboard for self–administration or can be read aloud to the respondent either in person or over the phone. It is preferable to administer the AD8 to an informant, if available. If an informant is not available, the AD8 may be administered to the patient.

When administered to an informant, specifically ask the respondent to rate change in the patient.

When administered to the patient, specifically ask the patient to rate changes in his/her ability for each of the items, ***without*** attributing causality.

If read aloud to the respondent, it is important for the clinician to carefully read the phrase as worded and give emphasis to note changes due to cognitive problems (not physical problems). There should be a one second delay between individual items.

No timeframe for change is required.
The final score is a sum of the number items marked "Yes, A change".

Interpretation of the AD8
(Adapted from Galvin JE et al, The AD8, a brief informant interview to detect dementia, Neurology 2005:65:559-564)

A screening test in itself is insufficient to diagnose a dementing disorder. The AD8 is, however, quite sensitive to detecting early cognitive changes associated many

common dementing illness including Alzheimer disease, vascular dementia, Lewy body dementia and frontotemporal dementia.

Scores in the impaired range (see below) indicate a need for further assessment. Scores in the "normal" range suggest that a dementing disorder is unlikely, but a very early disease process cannot be ruled out. More advanced assessment may be warranted in cases where other objective evidence of impairment exists.

Based on clinical research findings from 995 individuals included in the development and validation samples, the following cut points are provided:

- 0 – 1: Normal cognition
- 2 or greater: Cognitive impairment is likely to be present

Administered to either the informant (preferable) or the patient, the AD8 has the following properties:

- Sensitivity > 84%
- Specificity > 80%
- Positive Predictive Value > 85%
- Negative Predictive Value > 70%
- Area under the Curve: 0.908; 95% CI: 0.8880.9

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Appendix F: Charlson Comorbidity Index

Each item below receives 1 point unless stated otherwise

1. Myocardial Infarction
2. Congestive Heart Failure
3. Peripheral Vascular Disease
4. Cerebrovascular Disease
5. Dementia
6. COPD
7. Connective Tissue Disease
8. Peptic Ulcer Disease
9. Diabetes Mellitus (1 point uncomplicated, 2 points if end-organ damage)
10. Moderate to Severe Chronic Kidney Disease (2 points)
11. Hemiplegia (2 points)
12. Leukemia (2 points)
13. Malignant Lymphoma (2 points)
14. Solid Tumor (2 points, 6 points if metastatic)
15. Liver Disease (1 point mild, 3 points if moderate to severe)
16. AIDS (6 points)

Scoring: Age

1. Age <40 years: 0 points
2. Age 41-50 years: 1 point
3. Age 51-60 years: 2 points
4. Age 61-70 years: 3 points
5. Age 71-80 years: 4 points

Add co-morbidity scores to age score_____

Appendix G: APACHE II Severity of Disease Classification System

Physiologic Variable	High Abnormal Range					Low Abnormal Range				
	+4	+3	+2	+1	0	+1	+2	+3	+4	Points
Temperature - rectal (°C)	≥41°	39 to 40.9°		38.5 to 38.9°	36 to 38.4°	34 to 35.9°	32 to 33.9°	30 to 31.9°	≤29.9°	
Mean Arterial Pressure - mm Hg	≥160	130 to 159	110 to 129		70 to 109		50 to 69		≤49	
Heart Rate (ventricular response)	≥180	140 to 179	110 to 139		70 to 109		55 to 69	40 to 54	≤39	
Respiratory Rate (non-ventilated or ventilated)	≥50	35 to 49		25 to 34	12 to 24	10 to 11	6 to 9		≤5	
Oxygenation: A-aDO$_2$ orPaO$_2$ (mm Hg) a. FIO$_2$ ≥0.5 record A-aDO2 b. FIO$_2$ <0.5 record PaO2	≥500	350 to 499	200 to 349		<200 PO2>70	 PO2 61 to 70		 PO2 55 to 60	 PO2<55	
Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs)	≥7.7 ≥52	7.6 to 7.69 41 to 51.9		7.5 to 7.59 32 to 40.9	7.33 to 7.49 22 to 31.9		7.25 to 7.32 18 to 21.9	7.15 to 7.24 15 to 17.9	<7.15 <15	
Serum Sodium (mEq/l)	≥180	160 to 179	155 to 159	150 to 154	130 to 149		120 to 129	111 to 119	≤110	
Serum Potassium (mEq/l)	≥7	6 to 6.9		5.5 to 5.9	3.5 to 5.4	3 to 3.4	2.5 to 2.9		<2.5	
Serum Creatinine (mg/dl) Double point score for acute renal failure	≥3.5	2 to 3.4	1.5 to 1.9		0.6 to 1.4		<0.6			
Hematocrit (%)	≥60		50 to 59.9	46 to 49.9	30 to 45.9		20 to 29.9		<20	
White Blood Count (total/mm3) (in 1000s)	≥40		20 to 39.9	15 to 19.9	3 to 14.9		1 to 2.9		<1	
Glasgow Coma Score (GCS) Score = 15 minus actual GCS										
A. Total Acute Physiology Score (sum of 12 above points)										
B. Age points (years) ≤44=0; 45 to 54=2; 55 to 64=3; 65 to 74=5; ≥75=6										
C. Chronic Health Points (see below)										
Total APACHE II Score (add together the points from A+B+C)										

Chronic Health Points: If the patient has a history of severe organ system insufficiency or is immunocompromised as defined below, assign points as follows:

5 points for nonoperative or emergency postoperative patients
2 points for elective postoperative patients

***Definitions*:** organ insufficiency or immunocompromised state must have been evident **prior** to this hospital admission and conform to the following criteria:

- **Liver** – biopsy proven cirrhosis and documented portal hypertension; episodes of past upper GI bleeding attributed to portal hypertension; or prior episodes of hepatic failure/encephalopathy/coma.
- **Cardiovascular** – New York Heart Association Class IV.
- **Respiratory** – Chronic restrictive, obstructive, or vascular disease resulting in severe exercise restriction (i.e., unable to climb stairs or perform household duties; or documented chronic hypoxia, hypercapnia, secondary polycythemia, severe pulmonary hypertension (>40 mmHg), or respirator dependency.
- **Renal** – receiving chronic dialysis.
- **Immunocompromised** – the patient has received therapy that suppresses resistance to infection (e.g., immunosuppression, chemotherapy, radiation, long term or recent high dose steroids, or has a disease that is sufficiently advanced to suppress resistance to infection, e.g., leukemia, lymphoma, AIDS).

Interpretation of Score:

Score	Death Rate (%)
0-4	4
5-9	8
10-14	15
15-19	25
20-24	40
25-29	55
30-34	75
>34	85

Appendix H: Frailty Index

Change in activities of daily living	Abnormal sleep	Headaches
Head and neck condition	Restlessness	Cardiovascular disease
Incontinence	Short term memory difficulties	Stroke
GIT problems	Long term memory impairment	Diabetes
Mobility difficulties	Delirium	Peripheral vascular disease
Musculoskeletal condition	Paranoia	Cerebrovascular disease
Falls	Parkinson's disease	Myocardial infarction
Mood disturbance	Seizure disorder	Arrhythmia
Congestive cardiac failure	Respiratory disease	Thyroid disease
Skin problems	Malignancy	Breast disease
Visual impairment	Other illness	

Appendix I: Barthel Index

Patient Name: _____

Rater Name: _____

Date: _____

Activity	Score
FEEDING 0 = unable 5 = needs help cutting, spreading butter, etc., or requires modified diet 10 = independent	_____
BATHING 0 = dependent 5 = independent (or in shower)	_____
GROOMING 0 = needs to help with personal care 5 = independent face/hair/teeth/shaving (implements provided)	_____
DRESSING 0 = dependent 5 = needs help but can do about half unaided 10 = independent (including buttons, zips, laces, etc.)	_____
BOWELS 0 = incontinent (or needs to be given enemas) 5 = occasional accident 10 = continent	_____
BLADDER 0 = incontinent, or catheterized and unable to manage alone 5 = occasional accident 10 = continent	_____

TOILET USE

0 = dependent
5 = needs some help, but can do something alone
10 = independent (on and off, dressing, wiping) _____

TRANSFERS (BED TO CHAIR AND BACK)

0 = unable, no sitting balance
5 = major help (one or two people, physical), can sit
10 = minor help (verbal or physical)
15 = independent _____

MOBILITY (ON LEVEL SURFACES)

0 = immobile or < 50 yards
5 = wheelchair independent, including corners, > 50 yards
10 = walks with help of one person (verbal or physical) > 50 yards
15 = independent (but may use any aid; for example, stick) > 50 yards
_____

STAIRS

0 = unable
5 = needs help (verbal, physical, carrying aid)
10 = independent _____

TOTAL (0–100): _____

Provided by the Internet Stroke Center — www.strokecenter.org

The Barthel ADL Index: Guidelines

1. The index should be used as a record of what a patient does, not as a record of what a patient could do.
2. The main aim is to establish degree of independence from any help, physical or verbal, however minor and for whatever reason.
3. The need for supervision renders the patient not independent.
4. A patient's performance should be established using the best available evidence. Asking the patient, friends/relatives and nurses are the usual sources, but direct observation and common sense are also important. However direct testing is not needed.
5. Usually the patient's performance over the preceding 24-48 hours is important, but occasionally longer periods will be relevant.
6. Middle categories imply that the patient supplies over 50 per cent of the effort.
7. Use of aids to be independent is allowed.

References

Mahoney FI, Barthel D. "Functional evaluation: the Barthel Index." *Maryland State Medical Journal* 1965;14:56-61. Used with permission.

Loewen SC, Anderson BA. "Predictors of stroke outcome using objective measurement scales." *Stroke.* 1990;21:78-81.

Gresham GE, Phillips TF, Labi ML. "ADL status in stroke: relative merits of three standard indexes." *Arch Phys Med Rehabil.* 1980;61:355-358.

Collin C, Wade DT, Davies S, Horne V. "The Barthel ADL Index: a reliability study." *Int Disability Study.*1988;10:61-63.

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